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THIRTY-NINTH ANNUAL SESSION - ATLANTIC CITY, N. L., APRIL 28-MAY 2, 1958



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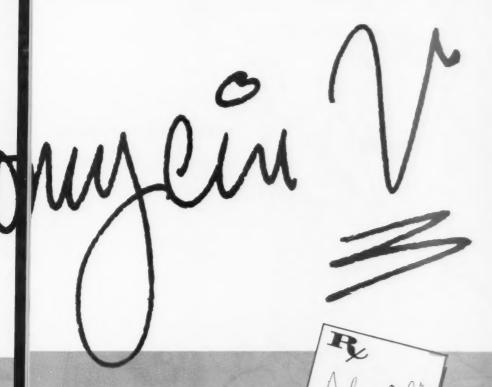
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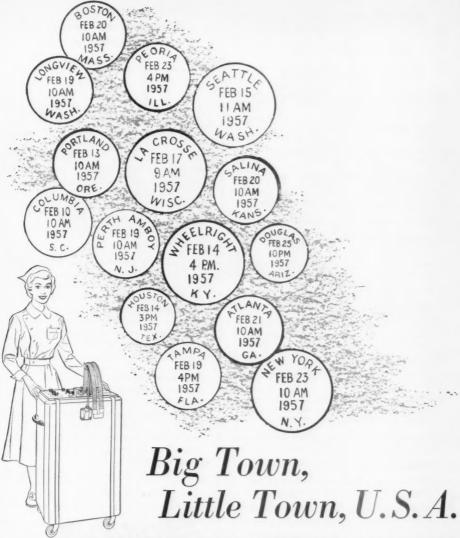
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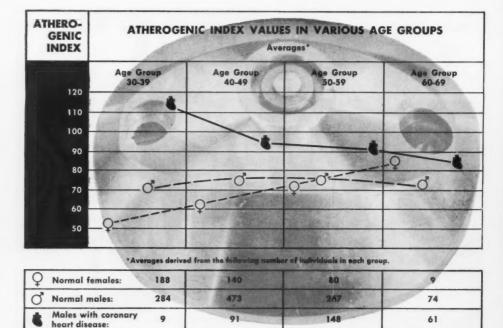
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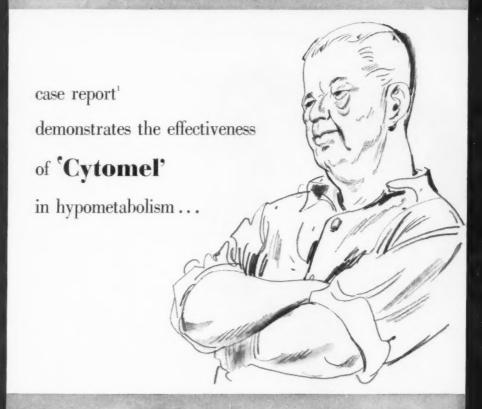
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1. Moyer, J.H.: J. Louisiana M. Soc. 108:231 (July) 1956.

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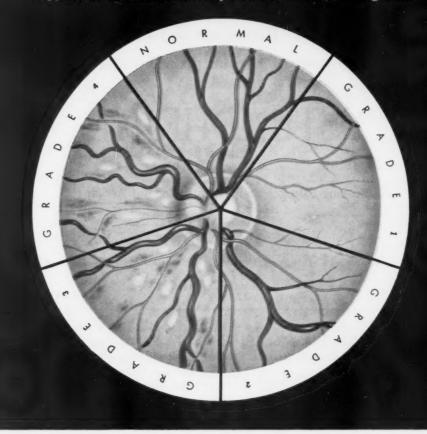
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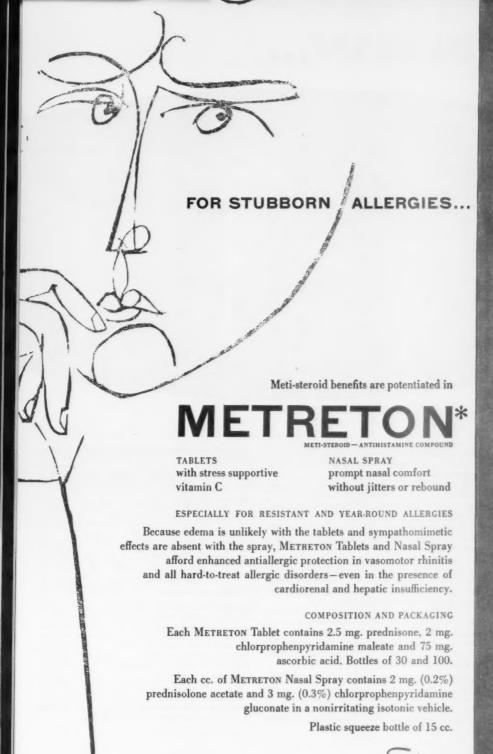
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INDICATIONS: A wide variety of conditions, in which four symptoms predominate: a) inflammation b) muscle spasm c) anxiety and tension d) discomfort and disability; i.e., rheumatoid arthritis, rheumatoid spondylitis (Marie-Strümpell disease), Still's disease, psoriatic arthritis, osteo-

Therapautic banefits of MEPROLONE compared with traditional antiarthritics.

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Muscle relaxants			1		
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Storoids	1	1			1
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1. Meprobamate is the only tranquilizer with muscle-relaxant action.

arthritis, bursitis, synovitis, tenosynovitis, myositis, fibrositis, fibromyositis, neuritis, acute and chronic low back pain, acute and chronic primary and secondary fibrositis and torticollis, intractable asthma, respiratory allergies, allergic and inflammatory eye and skin disorders (as maintenance therapy in disseminated lupus erythematosus, periarteritis nodosa, dermatomyositis and scleroderma).

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Multi-spectrum synergistically strengthened SIGMAMYCIN provides the antimicrobial spectrum of tetracycline extended and potentiated with oleandomycin to include even those strains of staphylococci and certain other pathogens resistant to other antibiotics.

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33 mg., tetracycline 67 mg.), bottles of 25 and 100. SIGMAMYCIN FOR ORAL SUSPENSION -1.5 Gm., 125 mg. per 5 cc. teaspoonful (oleandomycin 42 mg., tetracycline 83 mg.), mint flavored, bottles of 2 oz.

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†Cohen, B. M.; Cross, E. B., and Johnson W.: Am. Prac. & Digest Treat. 6: 1030, 1955.





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Cryptenamine......1.0 mg. (tannates)

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Bibliography. Orgain, E. S.: Postgrad, Med. 17: 318, 1955, Finnerty, F. A.: Am. J. Med. 17: 629, 1954. McCall, M. L.; Sass, D. K.; Wagstaff, C., and Cutler, J.: Obst. & Gynec. 6: 297, 1955. Cohen, B. M.: New York State J. Med. 55: 633, 1955. LaBarbera, J. F.: Med. Record and Annals 50: 242, 1955. Voskian, J.; Assail, M. S., and Noll, L.: Sarg., Gynec. & Obst. 102: 37, 1956. Crisp, W. E., and McCall, M. L.: Am. Prac. & Digost Treat, 7: 620, 1956. Finnerty, F. A.: Am. J. M. Sc. 229: 379, 1955.

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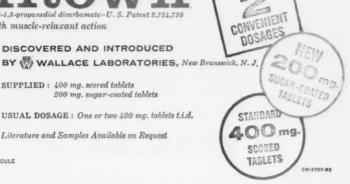
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5. Cass, L. J. & Wolf, L. P., Gastroenterology, 20:149, 1952

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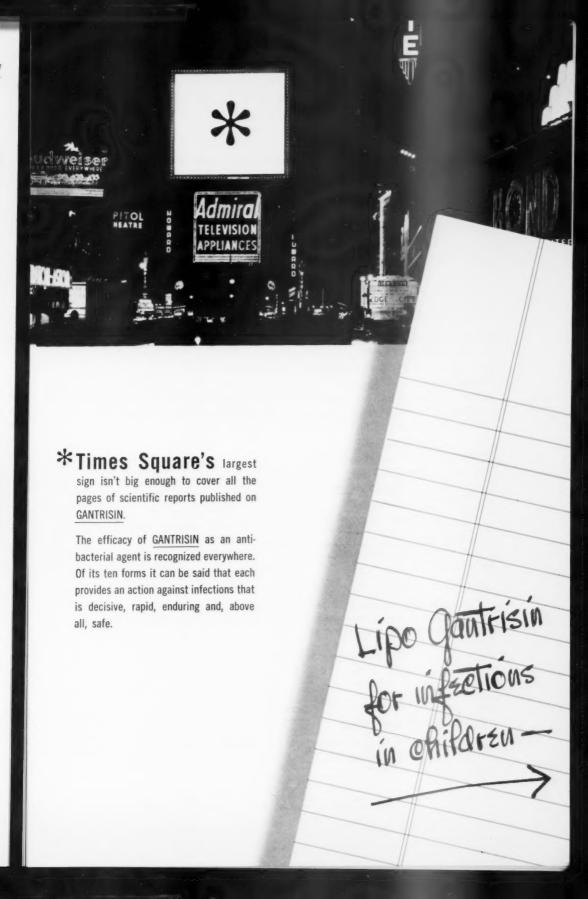
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DOSAGE:

Children:	teaspoonfuls every 12 hours	
20 lbs	1	CAUTION:
40 lbs	11/2	The usual precautions in sulfona-
60 lbs	2	mide therapy should be observed.
80 lbs	3	
Adults:	4	

SUPPLIED:

Lipo Gantrisin Acetyl, containing 20 per cent Gantrisin (1 Gm per 5 cc in the form of Gantrisin Acetyl), in a palatable, readily digestible homogenized emulsion that prolongs the action of the drug. In bottles of 4 and 16 oz.

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*Ferguson, J. T., and Linn, F. V. Z.: Antibiotic Med. & Clin. Therapy 3:329, 1956.



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NEW INTRAMUSCULAR IRON PROVIDES PRECISION THERAPY, PROMPT RESPONSE

IMFERON,® the new intramuscular iron-dextran complex, was introduced to American hematologists at the Sixth International Congress of the International Society of Hematology held in Boston, August 27 to September 1, 1956. Recent experience from over 6 million injections has shown that this iron preparation is easy to administer, notably free from toxic effects, quickly absorbed and productive of rapid hematologic and clinical improvement. It has been termed "... the only therapeutically effective iron preparation for intramuscular use...."1 IMFERON meets the need for a safe, effective agent when parenteral iron is preferable for patients with iron deficiency anemia who are resistant or intolerant to oral iron, those with depleted iron reserves and those who require rapid restoration of hemoglobin, e.g. last trimester of pregnancy.

Previous parenteral iron preparations were unsatisfactory because of toxicity, pain on injection, or because they contained insufficient iron. IMFERON contains the equivalent of 5 per cent elemental iron. It is more stable than iron saccharate both in vitro and in vivo and does not precipitate in plasma over a wide pH range. It is isotonic with tissue fluids and has a pH of 5.2 to 6.0¹ Utilization for hemoglobin formation is almost quantitative.

Precision Therapy with IMFERON: Before treating a patient with IMFERON, total iron requirement is calculated by formula or determined from a convenient dosage chart. Then appropriate amounts of IMFERON are injected daily or every other day, until the total calculated required amount is given.

Iron Deficiency Anemia of Infancy: IMFERON provides a convenient safe means for restoring hemoglobin levels and iron reserves in anemic infants. Excellent results were obtained by Gaisford and Jennison² with IMFERON in 100 iron-deficient infants. From a pretreatment average of 54.5 per cent, hemoglobin levels rose to 87 per cent 10 weeks after the start of therapy.

References: (1) Brown, E. B., and Moore, C. V., in Tocantins, L. M.: Progress in Hematology, New York, Grune & Stratton, Inc., 1956, vol. I, p. 25. (2) Gaisford, W., and Jennison, R. F.: Brit. M. J. 2:700 (Sept. 17) 1955. (3) Wallerstein, R. O.: J. Pediat. 49:173, 1956. (4) Sturgeon, P.: Pediatrics 18:267, 1956. (5) Jennison, R. F., and Ellis, H. R.: Lancet 2:1245 (Dec. 18) 1954. (6) Scott, J. M., and Govan, A. D. T.: Brit. M. J. 2:1257 (Nov. 27) 1954. (7) Grunberg, A.,

Clinical improvement paralleled this response. Premature infants and surgical cases were similarly benefited. IMFERON gave "...all the advantages of transfusion or intravenous therapy without the disadvantages."2 There were no side effects in any of the infants treated. Wallerstein³ confirmed these results, furnishing evidence that IMFERON is well absorbed and appears in the bone marrow 12 to 24 hours after injection. Results are equal to those with intravenous saccharated iron oxide without the unpleasant side effects. Sturgeon showed that the first year's iron requirements in infancy can be supplied with three injections of IMFERON. Iron Deficiency Anemia of Pregnancy: Nausea precludes oral iron therapy in many anemic pregnant women. In those with severe anemia who are first seen late in pregnancy, prompt hemoglobin regeneration is unobtainable with oral iron. IMFERON produced prompt hemoglobin responses in anemia of pregnancy,5,6 the results being similar to those obtained with intravenous saccharated iron oxide. Side effects

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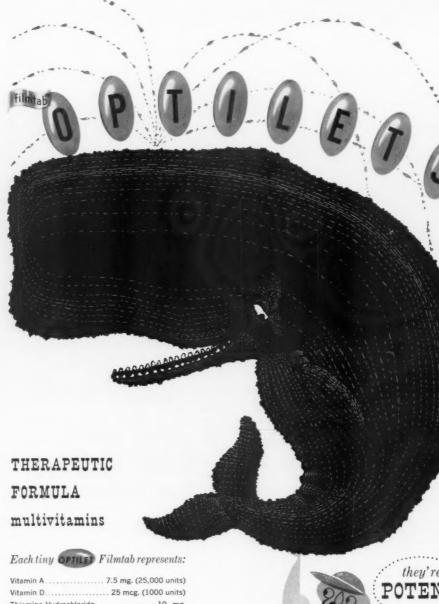
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and Blair, J. L.: A.M.A. Arch. Int. Med. 96:731, 1955. (8) Millard, J. B., and Barber, H. S.: Ann. Rheumat. Dis. 15:51, 1956. (9) Baird, I. M., and Podmore, D. A.: Lancet 2:942 (Nov. 6) 1954. (10) Cappell, D. F.; Hutchinson, H. E.; Hendry, E. B., and Conway, H.: Brit. M. J. 2:1255 (Nov. 27) 1954. (11) Stevens, A. R.: A.M.A. Arch. Int. Med. 96:550 1956.

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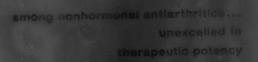
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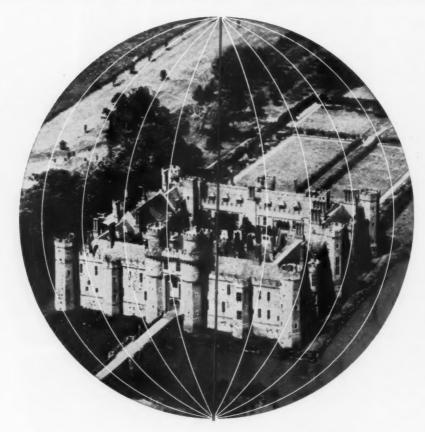
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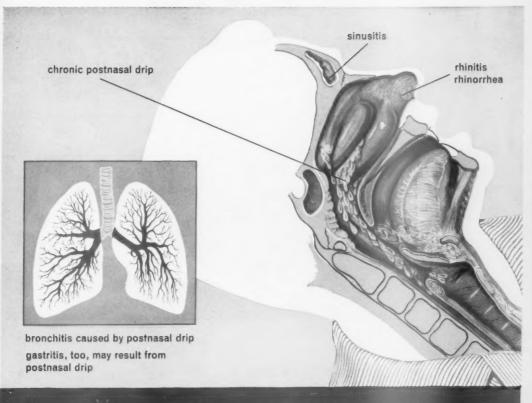
In 480 cases of Parkinsonism (arteriosclerotic, postencephalitic, and idiopathic), 50 investigators reported good to excellent results in 286 (59%), and fair in 97 (20.2%).

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maleate
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Professional literature available upon request.

1. Figurelli, F.A.: Indust. Med. & Surg. 25:376 (Aug.) 1956.

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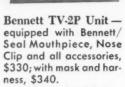
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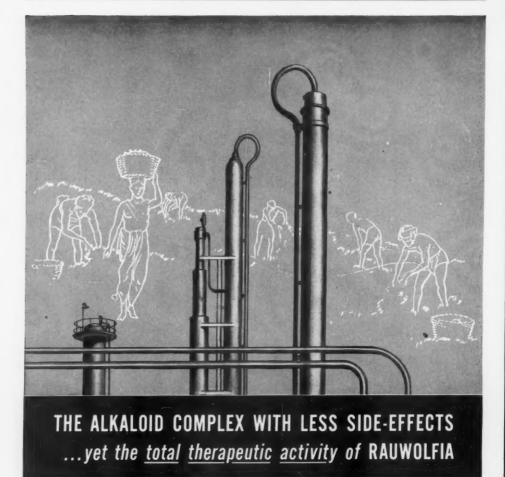
Bonamine affords a high degree of relief of vertigo in patients with cerebral manifestations. "The lack of adverse effects . . . suggests that long-term use of this drug . . . is a reasonable procedure in the management of such patients."3

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Bonamine is also valuable in treating the dizziness and emesis associated with radiation therapy, Ménière's syndrome, fenestration procedures, and labyrinthitis.

Available as scored, tasteless tablets, 25 mg.; and as mint-flavored chewing tablets, 25 mg.

Conner, P. K., Jr., and Moyer, J. H.: GP 16:124 (Nov.) 1956.
 Kinney, J. J.: J. M. Soc. New Jersey 53:128 (March) 1956.
 Weil, L. L.: Florida J. Gen. Pract. 6:9 (July) 1954.
 Report of Study by Army, Navy, Air Force Motion Sickness Team: J.A.M.A. 160:755 (March 3) 1956.



Rautensin provides all the essential antihypertensive alkaloids

Rautensin (the alseroxylon fraction complex of Rauwolfia) contains both rescinnamine and reserpine, together with the other valuable alkaloids.

Produces a gradual and sustained drop in blood pressure.

Calms and soothes the patient without loss of alertness.

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The alseroxylon fraction complex of Rauwolfia was found less prone to cause mental depression.

Does not usually cause drowsiness.

Is purified and is therefore free of inert dross present in the whole root.

1. Moyer, J.H.; Dennis, E., and Ford, R.: A.M.A. Arch. Int. Med. 96: 530, 1955

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Each tablet contains 2 mg. purified Rauwolfia serpentina alkaloids (alseroxylon fraction)

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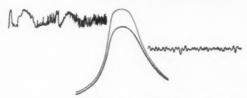
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"... after the proper dose was established, 'Mysoline' was well tolerated without [serious] side effects."3

- Doyle, P. J., and Livingston, S.: J. Pediat. 43:413 (Oct.) 1953.
 Livingston, S., and Petersen, D.: To be published.
 Pence, L. M.: Texas State J. Med. 50:290 (May) 1954.

LITERATURE ON REQUEST

Supplied: Tablets, 0.25 Gm. Bottles of 100 and 1,000. Suspension, 0.25 Gm. per 5 cc. (teaspoonful). Bottles of 8 fluidounces.

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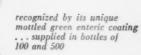
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> *Schwab, R. S., and Leigh, D., J.A.M.A. 139:629, 1949.

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FOR SEVERE-INCLUDING MALIGNANT-HYPERTENSION

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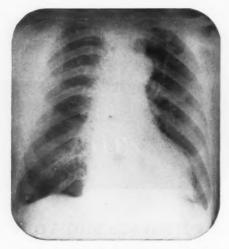
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ROENTGEN CONFIGURATION

Postero-anterior position

Moderate left ventricular enlargement with prominence and calcification of aortic knob.

Taken from White Laboratories' Technical Exhibit, American Medical Association, 105th Annual Meeting, Chicago, June 11-15, 1956.



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Patients now on other cardiotonics may be easily maintained on Gitaligin: 0.5 mg. of Gitaligin is approximately equivalent to 0.1 Gm. digitalis leaf, 0.1 mg. digitoxin, 0.5 mg. digoxin.

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*HARRIS, R., AND DEL GIACCO R. R.: AM HEART J. (AUG.) 1956, BIBLI-OGRAPHY ON REQUEST



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(WHITE'S BRAND OF AMORPHOUS GITALIN

White Laboratories, Inc. . Kenilworth, New Jersey

One of the safest, least toxic and most effective therapeutic agents for many conditions in which the weaker tranquilizers or sedatives are inadequate

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alcoholism			5	5
pediatric emotional problems	ric emoti	pedi	5	5
acute psychotic disturbances	psychotic	acut	5	5

side effects and precautions

in hypertension



Serpasil® can always be considered first

- BECAUSE alone: Serpasil successfully reduces blood pressure, slowly and safely, in about 70 per cent of cases of mild to moderate hypertension.¹
- **BECAUSE** as a "primer": Serpasil may be advantageously used to begin antihypertensive therapy, however severe the case, since it gently adjusts the patient to the physiologic setting of lower pressure.
- as a "background" agent throughout other therapy: Serpasil permits lower dosage of the more potent antihypertensives needed for refractory cases, thus minimizing the incidence and severity of side effects.

USUAL DOSE: Initially, two 0.25-mg. tablets. After a week, daily dose should be reduced to 0.25 mg. or less for maintenance.

"...a useful agent for the treatment of certain types of hypertension....The action...was increased by combining it with [Apresoline]..."²

Coan, J. P., McAlpine, J. C., and Boone, J. A.: J. South Carolina M. A. <u>51</u>:417 (Dec.) 1955.
 Winsor, T.: Ann. New York Acad. Sc. 59:61 (April 30) 1954.

in emotional disorders



Serpasil[®] provides true emotional control

In your daily practice there are undoubtedly many patients whose degree and type of emotional disturbance—characterized by overexcitation, anxiety and agitation—can not be adequately controlled with sedatives or weaker tranquilizers. These are the patients whom you can help most with once-a-day administration of Serpasil. For Serpasil actually sets up a "stress barrier" against anxiety and tension the patient would otherwise find intolerable. With Serpasil you can control the emotional turmoil of disturbed individuals; and because Serpasil is restricted to prescription use, control remains in your hands.

Although it is a first choice in hypertension, Serpasil does not significantly lower blood pressure in normotensive patients.

USUAL DOSE: Initial range is 0.1 mg. to 0.5 mg. (two 0.25-mg. tablets) daily. As little as 0.1 mg. is sufficient for maintenance in some patients. Serpasil can be given in a single daily dose.

"... relieves anxiety and irritability and calms the patient so effectively that because of this latter property alone, the drug should remain in the medicinal armamentarium."

in tachycardia



Serpasil® slows the rapid heart

Many patients can benefit from the heart-slowing action of Serpasil. Those in whom tachycardia is deleterious are helped by its unique bradycardic effect, for Serpasil prolongs diastole and allows more time for the myocardium to rest. Blood flow and cardiac efficiency are thus enhanced.

USUAL DOSE: 0.1 mg. to 0.5 mg. (two 0.25-mg. tablets) daily. After one or two weeks dose may be reduced.

"Reserpine [Serpasil] was found useful in relieving the tachycardia and emotional symptoms associated with cardiac arrhythmias, thyrotoxicosis, neurocirculatory asthenia, and even coronary heart disease."

Halprin, H.: J. M. Soc. New Jersey 52:616 (Dec.) 1955.

in acute hypertensive crises



Parenteral Serpasil

Serpasil can be used alone in hypertensive emergencies or as a background to more potent antihypertensive agents. Its antihypertensive action is prompt and well-tolerated.

 $\tt USUAL\ DOSE$: 2.5 mg. (1 ml.) intramuscularly. Additional intramuscular doses of 2.5 mg. may be given as necessary every 8 to 24 hours.

"... appears to be [a] treatment of choice for hypertensive crises."

in alcoholism



Serpasil® relieves drink-inducing tension

As a part of long-term therapy, oral Serpasil helps the alcoholic "stay on the wagon" by relieving drink-inducing tension, making him more amenable to your counseling.

In acute alcoholism, delirium tremens can generally be controlled within 24 hours with parenteral Serpasil...without the addicting or soporific dangers of drugs such as paraldehyde.

USUAL DOSE: Chronic phase: two 0.25-mg. tablets or less daily. Acute phase: two 2.5-mg. parenteral doses (1 ml. each) 3 or more hours apart. Occasionally, repeat injections of 2.5 mg. every 4 to 6 hours may be necessary.

"...the tranquilizing and anxiety-relieving properties of this drug [Serpasil] offer the possibilities of its being extremely helpful for the long-term therapy of the chronic alcoholic."

Greenfield, A. R.: Am. Pract. & Digest Treat. 7:241 (Feb.) 1956.

in pediatric emotional problems



Serpasil Elixir benefits the "problem child"

Serpasil provides a shield against stress in the overreactive, tense, "problem child." Striking remissions have been observed in children with excessive crying, poor eating and sleeping patterns.

USUAL DOSE: 0.1 to 0.3 mg. daily ($\frac{1}{2}$ to $\frac{1}{2}$ teaspoons of Serpasil Elixir, 0.2 mg. per 4-ml. teaspoon).

"...provided dramatic relief in remitting the syndrome of irritability in 29 of the 32 cases studied..."

Talbot, M. W., Jr.: Ann. New York Acad. Sc. 61:188 (April 15) 1955.

in acute psychotic disturbances



Parenteral Serpasil

The family physician is often called to subdue and arrange for quick hospitalization of patients who suddenly experience violent psychotic episodes. With intramuscular Serpasil these patients are quickly tranquilized and rendered amenable to 'quiet' hospitalization.

USUAL DOSE: 5 mg.intramuscularly followed, if necessary, by another 5-mg.intramuscular dose in 90 minutes.

"It is now possible to discreetly manage acutely disturbed psychiatric patients by the prompt administration of adequate doses of reserpine (Serpasil)."

Ayd, F. J., Jr.: The Pharmacologic Management of Everyday Psychiatric Problems (A Scientific Exhibit).

Presented at the Clinical Meeting of the American Medical Association, Boston, Mass., Nov. 29-Dec. 2, 1955.

Serpasil:

side effects and precautions

The side effects of Serpasil are characteristic of all rauwolfia preparations.

Although millions of patients have taken Serpasil over the past several years, very few serious side reactions have been reported. There have been no cases of blood dyscrasia, liver damage, addiction or withdrawal symptoms. When patients are properly selected and the lowest effective maintenance dose is established, the physician can prescribe Serpasil confidently, with little fear of untoward reactions.

Depression

Mental depression, which has developed in a small percentage of patients treated with rauwolfia, should be differentiated from the transient change in mood or physical fatigue that is experienced by almost everyone in the general population. It should also be distinguished from the lethargy experienced by some patients on rauwolfia therapy.

In the few cases in which mental depression does occur, there is some question as to whether or not it is a direct effect of rauwolfia, According to Mayo Clinic investigators,1 the evidence indicates that rauwolfia per se does not cause depression, but rather that it unmasks an underlying susceptibility to depressive reactions. Kinross-Wright² states: "It is likely that depression will occur only in a predisposed individual or in one who is already mildly depressed." Ayd,3 in a very recent paper, states: "That this drug may cause depression is uncertain. After reviewing a large number of socalled drug-induced depressions it appears that in some cases what was called depression was excessive tranquilization, while in the rest, the patients were depressed before the drug was started, and what the drug did was make the depression more apparent."

Whether or not it is an effect of rauwolfia, physicians and responsible members

of the patient's family should be on the alert for the development of symptoms of depression, particularly in patients with a history of pre-existing depressive tendencies. Daily doses above 0.25 mg. are contraindicated in the latter group. On withdrawal of rauwolfia, depression usually disappears, but active treatment, including hospitalization for shock therapy, has been required in some cases.

Adjunctive use of mood-elevating agents such as Ritalin is often sufficient to reverse mild depressions or drug-induced lethargy.

Other side effects

In addition to lassitude or drowsiness, other mild side effects of Serpasil include occasional nasal stuffiness and increased frequency of defecation and/or looseness of stools. Rarely, anorexia, headache, bizarre dreams, nausea and dizziness occur. With parenteral Serpasil there is a possibility of marked hypotensive effect; therefore, the blood pressure should be taken before injection and the patient kept under observation for 5 or 6 hours thereafter. Because initial doses above 0.3 mg. tend to increase gastric secretion of hydrochloric acid, daily doses above 0.25 mg. are contraindicated in patients with a history of peptic ulcer and lower doses should be used with caution.

For further details on side effects and precautions, write Medical Service Division.

1. Litin, E. M., Faucett, F. L., and Achor, R. W. P.: Proc. Staff Meet., Mayo Clin. 31:233 (April 18) 1956.

 Kinross-Wright, V.: Wisconsin M. J. 55:1073 (Oct.) 1956.
 Ayd, F. J., Jr.: Presented at the Sesquicentennial Convention of The Medical Society of The State of New York, New York City, Feb. 18, 1957.

SUPPLIED:

TABLETS, 0.1 mg., 0.25 mg., 1 mg., 2 mg. and 4 mg. ELIXIRS, 0.2 mg. and 1 mg. per 4-ml. teaspoon.

PARENTERAL SOLUTION: Ampuls, 2 ml., 2.5 mg. Serpasil per ml. Multiple-dose Vials, 10 ml., 2.5 mg. Serpasil per ml.

APRESOLINE® hydrochloride (hydralazine hydrochloride CIBA) RITALIN® hydrochloride (methylphenidate hydrochloride CIBA)

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initial tetracycline blood levels

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a single antibacterial antibiotic

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			May				June			
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Course No. 3, INTERNAL MEDICINE: The University of Chicago Department of Medicine, Chicago, Ill.; Wright Adams, M.D., F.A.C.P., Director, and Robert G. Page, M.D., Co-director.		X			N. Y.					
Course No. 4, EARLY DETECTION AND PREVENTION OF DISEASE: University of Pennsylvania School of Medicine, Department of Public Health and Preventive Medicine, Philadelphia, Pa.; John P. Hubbard, M.D., F.A.C.P., and Norbert J. Roberts, M.D., F.A.C.P., Co-directors.			X		ew York,					
Course No. 5, INTERNAL MEDICINE: Louisiana State University School of Medicine, Postgraduate Division, Shreveport, La.; Edgar Hull, M.D., F.A.C.P., and Marion D. Hargrove, M.D., F.A.C.P., Co-directors.			X		Meeting, N					
Course No. 6, CARDIOLOGY: The National Institute of Cardiology of Mexico, Mexico, D. F.; Ignacio Chávez, M.D., F.A.C.P., Director.				x						
Course No. 7, INTERNAL MEDICINE: New York University Post-Graduate Medical School, New York, N. Y.; Charles F. Wilkinson, Jr., M.D., F.A.C.P., and Clarence E. de la Chapelle, M.D., F.A.C.P., Co-directors.				X	I.A. Annual					
Course No. 8, BALLISTOCARDIOGRAPHY: University of Pennsylvania School of Medicine, Philadelphia, Pa.; Isaac Starr, M.D., Director.					A.M	10-12				

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*Holly, R. G.: Iron and Cobalt in Pregnancy, Obst. & Gynec. (Mar.) 1957.

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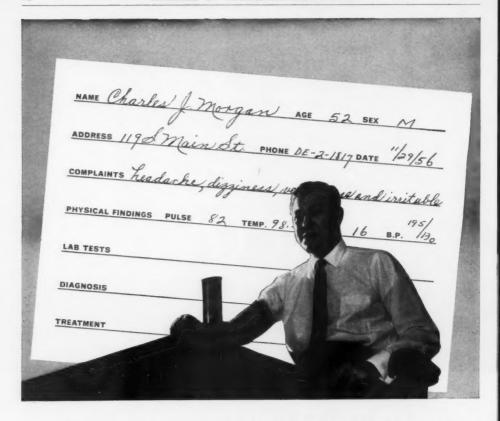
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LaBarbera, J.F.: Med.Rec. & Ann. 50:242, 1956.
 Ledbetter, P.V., and Morrow, E.J.: J. Am. Geriatries Soc. 3:172 (March) 1955.
 Wilkins, R.W.: Am. J. Med. 17:703 (Nov.) 1954.
 Moyor, J.H.: Dennis, E., and Ford, R.: A.M.A. Arch. Int. Med. 96:530, 1955.

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*Stein, I.: Annals of Internal Medicine 45:185, 1956.

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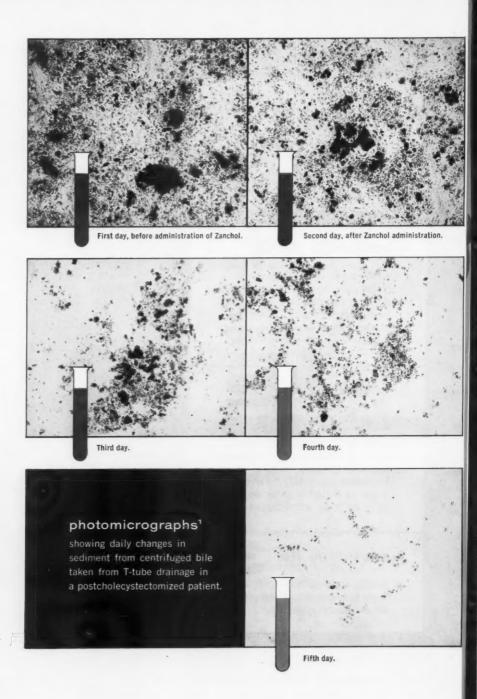
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 McGowan, J. M.: Clinical Significance of Changes in Common Duct Bile Resulting from a New Synthetic Choleretic, Surg., Gynec. & Obst. 103:163 (Aug.) 1956.

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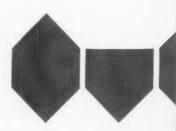
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Announcing a unique new rauwolfia derivative...



First report on one of the most encouraging advances in psychopharmacology since the introduction of rauwolfia:

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In mid-1955, Abbott Laboratories released for clinical trial a new alkaloid of *Rauwolfia canescens*. This new alkaloid, later named Harmonyl, received special attention because of the high potency and low toxicity it exhibited in pharmacological testing.

Since that time, Harmonyl has been tried in conditions ranging from mild anxiety to major mental illnesses and in hypertension. Every characteristic of the drug was studied . . . evaluated . . . compared. And from the reports, one fact stands out:

- In more than two years of clinical trials, Harmonyl has exhibited significantly fewer and milder side effects in comparative studies with reserpine. This, while demonstrating effectiveness comparable to the most potent forms of rauwolfia.
- Most significant: Harmonyl causes less mental and physical depression. And there are very few reports of the lethargy seen with many other rauwolfia preparations.

This is not to suggest, of course, that side effects will not occur with Harmonyl—as with any potent therapeutic agent. But the mildness of side effects, in the few instances in which they have been reported, suggests Harmonyl as a drug of choice in conditions ranging from mild anxiety to major mental illness and in hypertension.

Why fewer and less severe side effects?

Some investigators suggest that the evidence of less parasympathetic effect with Harmonyl in animals might also be true in man. In chronic toxicity studies with Harmonyl this was manifested by less diarrhea, "bloody tears" and ptosis in rats than was observed with the same dosage level of reserpine. Dogs also exhibited milder side effects—in particular, diarrhea. No organ toxicity or hematological change occurred over a wide dosage range.

Harmonyi as a tranquilizer

While Harmonyl's safety is most impressive, clinical investigators have reported other notable characteristics for this wide-range tranquilizer. For instance, following an eightmonth study of chronic, hospitalized mental patients, Ferguson' reported:

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Harmonyl benefited at least 15% more overactive patients than oral reserpose.

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In his summary, Ferguson concluded: "The most notable impressions were the absence of side effects and relatively rapid onset of action with Harmonyl."

Harmonyl in hypertension

Hypertension studies show that the average reduction in blood pressure obtained with Harmonyl compares closely to that obtained with reserpine. The tranquilizing effect of the two drugs also appeared similar, except that few cases of giddiness, vertigo, sense of detached existence or disturbed sleep were seen with Harmonyl.

Dosages In mild anxiety, as little as 0.1 mg. of Harmonyl a day may be effective. In institutionalized psychiatric patients, not less than 2 to 3 mg. a day is likely to be beneficial.

In mild essential hypertension, treatment may be started with one 0.25 mg. Harmonyl tablet three or four times a day. After about ten days (or sooner, depending upon response), dosage may be reduced. A maintenance dose of 0.25 mg. daily is often sufficient.

Precautions, Contraindications As with other forms of rauwolfia, Harmonyl must be used cautiously in peptic ulcer and epilepsy and in patients about to undergo surgery or electroshock treatment. Despite the infrequency of reports involving depression, patients with a history of depressive episodes should be watched carefully.

Professional literature is available upon request.

Supplied: Harmonyl is supplied in 0.1-mg., 0.25-mg. and 1-mg. tablets.

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Reference: 1. Ferguson, J. T. Comparison of Reserpine and Harmonyl in Psychiatric Patients: A Preliminary Report, Journal Lancel, 76:389, December, 1956.



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- 1. Quinn, E.L., et al.: J.A.M.A. 160:931 (March 17) 1956.
- Cox, F., Jr., et al.: Fourth Annual Symposium on Antibiotics, Washington, D.C., October 17, 1956.

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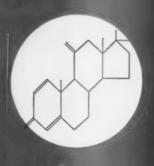
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1. Bollet, A.J., Black, R., and Bunim, J.J.: J.A.M.A. 158:459 (June 11) 1955.



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ANNALS OF INTERNAL MEDICINE

VOLUME 46

JUNE, 1957

NUMBER 6

ACUTE PEPTIC ULCERATION FOLLOWING CARDIAC SURGERY *

By Donald Berkowitz, M.D., Bernard M. Wagner, M.D., and Joseph F. URICCHIO, M.D., Philadelphia, Pennsylvania

A VARIETY of stressful stimuli when applied to a susceptible host have been recorded as provoking an ulcerative response in the gastrointestinal tract. Thus burns,1-4 trauma,5-9 central nervous system disease 10-20 and fractures 21 have been implicated in the past.

Surgery in particular has been well documented as an ulcerogenic stimu-1115 5, 6, 9, 22-30

Recently, surgical technics have been developed for the therapy of many congenital and acquired heart lesions. As a general experience, these measures are exceptionally complicated and have been applied to patients chronically and severely ill. Thus the combination of a severely traumatic experience applied to a host with serious, long-standing disease would, on superficial examination, appear to fulfill the requirements for an exceptionally stressful and possibly ulcerogenic agent.

This report confirms the latter impression, and presents seven cases of acute peptic ulceration occurring after cardiac surgery. Six of the patients had a massive gastrointestinal hemorrhage, the other a perforation. Four of the cases were studied histologically, and form the basis of this report. In the remaining three the clinical course, despite the absence of tissue confirmation, led us to believe that we were dealing with an acute peptic ulcer.

CASE REPORTS

Case 1. A 65 year old white male was admitted for surgical repair of a left ventricular aneurysm which had resulted from a myocardial infarction five years previously. He gave a history of having had a duodenal ulcer many years before.

*From the Symposium on Gastroduodenal Ulcer, presented at the Thirty-eighth Annual Session of The American College of Physicians, Boston, Massachusetts, April 11, 1957.

From the Departments of Medicine and Thoracic Surgery, Hahnemann Medical College and Hospital, and the Bailey Thoracic Clinic, Philadelphia, Pennsylvania.

Requests for reprints should be addressed to Donald Berkowitz, M.D., Temple Uni-

versity Hospital, Broad and Ontario Streets, Philadelphia 3, Pennsylvania.

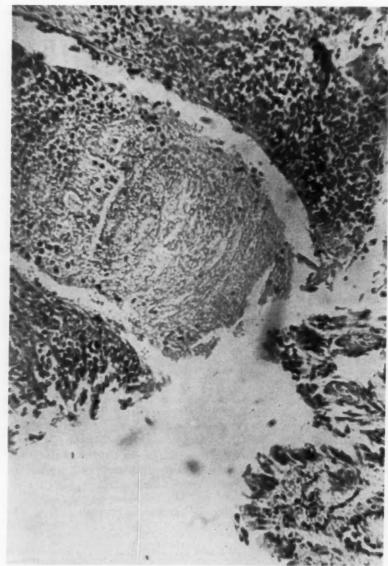


Fig. 1. The duodenal mucosa is acutely ulcerated and a large blood clot is noted opening into the lumen (hematoxylin and eosin stain \times 200).

Following excision of the aneurysm the immediate postoperative course was uneventful. On the eighth day the patient began to have melena, continued to bleed from the rectum, and died of exsanguination 12 hours later.

Autopsy revealed the presence of three distinct areas of ulceration, one in the prepyloric region and two in the duodenum. The prepyloric ulcer was sharply delineated, measured 1.8 cm. in diameter and extended from the greater curvature to the pylorus. One of the duodenal ulcers was located on the anterior wall and appeared to have perforated. The other ulcer was 3.5 cm. from the pylorus on the inferior anterior aspect of the duodenum.

Histologic examination of the lesions revealed an acute inflammatory process with ulceration of the mucosa down to the muscularis. No evidence of fibroblastic proliferation or chronic inflammatory reaction was noted (figure 1).

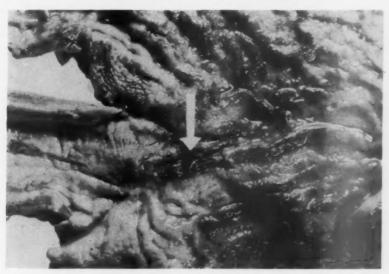


Fig. 2. Acute bleeding ulcer of stomach. (Head of arrow points to site of active hemorrhage.) Lesion located near cardia.

Case 2. A 43 year old white female was admitted with symptoms referable to mitral stenosis of long duration. Three years before she had sustained an embolism of a mesenteric vessel.

Nine days after admission a mitral commissurotomy was performed.

Immediately following surgery severe hypotension developed and persisted for 24 hours. The temperature rose to 104° F., and upper right quadrant pain and abdominal distention were present. Peristalsis could not be detected. A diagnosis of a mesenteric artery embolus was made and a laparotomy was done. A large area of hemorrhagic infarction of the jejunum and ileum was found. Due to the critical condition of the patient, no definitive surgical procedure was carried out. Soon afterward it was noted that blood was being aspirated from the stomach through the Wangensteen apparatus. The patient then went into shock and died.

Autopsy revealed a large gastric ulcer on the lesser curvature of the stomach (figure 2). The ulcer bed contained small blood clots as evidence of active hemorrhage. Histologic study indicated an acute ulcerative process.



The smaller vessels of the duodenal mucosa are congested and on the left there is erosion of the epithelial surface associated with bleeding (hematoxylin and eosin stain $\times 175$). 3 F16.

Case 3. A 40 year old white male was admitted with a history of rheumatic fever at age 14, and the onset of progressive exertional dyspnea at age 27. Physical findings indicated mitral and aortic stenosis. A mitral and aortic commissurotomy

was performed, with no complications.

Postoperatively the patient's course was completely uneventful until the seventh day, when massive hematemesis occurred. Because of continued bleeding, surgical intervention became necessary. At operation, the entire gastric mucosa was covered by petechial hemorrhages ranging in size from pinpoint to 0.3 cm. A subtotal gastrectomy was done. Microscopic examination revealed multiple focal erosions of the gastric mucosa with extensive extravasation of capillary blood (figure 3).



Fig. 4. Perforated gastric ulcer located near pylorus. Friable clot may be noted in the center of the ulcer.

Case 4. A 55 year old white male was admitted with signs and symptoms of mitral insufficiency. At operation this was confirmed and a commissurorrhaphy was done. Postoperatively he complained of persistent right upper quadrant pain. On the third day the pain became more severe, and dyspnea and cyanosis were noted. Soon afterward no pulse or blood pressure could be obtained. Cardiac massage was rapidly undertaken but was unsuccessful.

Autopsy revealed a generalized purulent peritonitis resulting from a large perforated ulcer on the posterior aspect of the stomach near the pylorus (figure 4).

Microscopic sections showed this to be an acute ulcer.

Case 5. A 47 year old white male was admitted to the hospital because of angina and progressive heart failure. The physical findings were those of pure aortic stenosis.

Cardiac catheterization corroborated this diagnosis.

An aortic commissurotomy was done through a right-sided thoracic approach, using a transaortic technic. On the third postoperative day the patient began to pass tarry stools and to complain of epigastric tenderness. The hemoglobin fell from 14 to 9 gm. Vigorous therapy consisting of whole blood transfusions, strict ulcer diet, antacids and anticholinergic drugs was instituted, with cessation of the bleeding.

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Case 6. A 31 year old white male was admitted for cardiac surgery because of fatigue, vertigo and progressive dyspnea. The blood pressure was 122/40 mm. of Hg, and there were murmurs of mitral stenosis and aortic insufficiency.

At operation the mitral valve was markedly stenosed and calcified, and a commissurotomy was done. The aortic valve was then explored from above. This was found to be incompetent, and a nylon peduncle was inserted in an attempt to correct the insufficiency.

The postoperative course was especially stormy and was complicated by dyspnea and persistent tachycardia. On the tenth day the patient became cyanotic, the blood pressure fell, and he began to pass large amounts of dark blood by rectum. In spite of many transfusions the bleeding continued and he died.

Case 7. A 28 year old white male was admitted with mitral stenosis and insufficiency. At operation the mitral valve was markedly regurgitant with but minimal stenosis. A suture of the valve (Nichols' procedure 31) plus a commissurotomy was performed, with no complications. Postoperatively the course was uneventful until the fourth day, when massive melena was noted and the hemoglobin fell to 8 gm. The possibility of a "stress ulcer" was considered and the patient was put on a strict ulcer regimen, with rapid blood replacement. A total of 15 pints of blood was given over the next 48 hours, after which the bleeding stopped. An emergency upper gastrointestinal x-ray was done, but revealed no gross evidence of an ulcer.

The patient was discharged asymptomatic 10 days later.

DISCUSSION

The exact mechanism responsible for acute ulceration of the gastrointestinal tract following surgery is not well understood.

Early theories suggested a neurogenic mechanism involving the hypothalamus and the vagal nerves.¹⁰

Hypotension with resulting ischemia has also been implicated in the pathogenesis. Thus, Selye has shown that various stresses may produce an alarm reaction, and during the shock phase acute gastrointestinal ulcers may form.³² In two of our cases, prolonged hypotension was present during the operative procedure and immediately following surgery.

More recent work in keeping with current concepts of the hypothalamuspituitary-adrenal axis postulates a humoral component. Thus, Hume,³³ Gray,³⁴ Moore ³⁵ and Shay ^{36, 37} have advanced a schema whereby the hypothalamus, in response to stress, secretes a humoral substance which stimulates the pituitary to release corticotropin. This in turn activates the adrenal cortex and corticoids are produced which then stimulate the gastric glands to secrete hydrochloric acid and pepsin.

As a result of our studies, several points must be emphasized. Acute gastrointestinal ulceration occurring after cardiac surgery is a serious complication. Four of the patients died as a direct result, and another survived only because of emergency gastric surgery.

The second important point to note is that this complication arises without any obvious background and without any prodromata—melena, hema-

temesis, or shock being the initial finding. In the case with perforation, persistent abdominal pain with progressive rigidity was significant, but was clinically misinterpreted. Only one of the patients (case 1) had a previous ulcer background, and even in this case the source of his fatal hemorrhage was a new lesion in the stomach. The original site of ulceration was not even grossly apparent.

Arising without a background and without prodromata, acute ulceration of the gastrointestinal tract therefore assumes an important position as one of the possible causes of undiagnosed shock in the postoperative cardiac patient. Examinations of the abdomen as well as the heart and lungs must therefore be made frequently, and even a rectal examination may at times be indicated to detect melena.

Until such time as we can predict who will develop these so-called "stress ulcers," the physician must always be on the alert for this possibility. This is especially true for those patients who have already demonstrated an abnormal response to stress in the past.

Acute ulceration occurring without clinical bleeding or perforation is much more common than is generally supposed. In a study of a group of patients who died following cardiac surgery from various causes, necropsy findings revealed an incidence of acute ulcerative lesions of the gastrointestinal tract of greater than 15%. Had these patients lived longer they might have manifested symptoms.

The treatment of acute gastrointestinal hemorrhage or perforation must be prompt in these cases. Immediate transfusions and early surgery may be lifesaving, in contrast to the outcome of the more conservative attitude of watchful waiting, frequently applicable to the chronic ulcer.

SUMMARY

Acute peptic ulceration following cardiac surgery has been demonstrated in four patients and clinically suspected in three others. This is a most serious complication, four of the cases having died as a direct result. Another survived only after emergency gastric resection. Prompt diagnosis is essential for a favorable outcome and may be attained only by a constant alertness to the possibility of an acute ulcer in any postoperative cardiac patient who is not doing well. Early surgery, rather than a more conservative program of therapy, may be lifesaving in these cases and should not be withheld merely because the patient has recently undergone cardiac surgery.

ACKNOWLEDGMENT

Sincere appreciation is expressed to Dr. Robert Glover for permission to include the first case.

SUMMARIO IN INTERLINGUA

Un varietate de stressose stimulos ha essite reportate como factores capace a evocar responsas ulcerative in le vias gastrointestinal. Assi, ulceres acute ha essite associate con arditura, trauma, morbo de systema nervose central, fractura, e chirurgia.

In recente tempores, nove technicas operatori ha essite disveloppate pro le tractamento de multe congenite e acquirite lesiones cardiac. Iste technicas require exceptionalmente complicate manovras, e le combination de chirurgia traumatic con le stato seriemente morbide del patiente pare certo satisfacer le criterios de un stimulo stressose e ulcerogene.

Iste reporto confirma le supra-mentionate these e presenta septe casos de acute ulceration peptic occurrente post chirurgia cardiac. Sex del septe patientes habeva massive hemorrhagias gastrointestinal, le septime habeva un perforation. Quatro del patientes moriva, e un quinte superviveva solmente post un urgente resection gastric. Le examine histologic del necropsiate o resectionate specimens monstrava que le ulceres esseva processos acute.

Tal "ulceres de stress" es un serie complication de chirurgia cardiac, como es evidente per le alte mortalitate in iste gruppo. Un prompte diagnose es de importantia cardinal pro un resultato favorabile e pote esser assecurate solmente per le continue e semper vive attention prestate al possibilitate del disveloppamento de ulceres acute in post-operatori patientes cardiac qui non progrede satisfactorimente. Un prompte intervention chirurgic, in loco de un plus conservative programma therapeutic, es possibilemente capace a salvar le vita del patiente e non deberea esser considerate como contraindicate solmente proque un patiente ha recentemente experientiate un operation cardiac.

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A STUDY OF THE RELATION OF THE ABO BLOOD GROUPS TO PEPTIC ULCERATION AND HYPERTENSION *

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THE relationship of the ABO blood groups to various diseases has received increasing attention of late. Thus, Aird et al.1 report that "the frequency of blood group A is greater and the frequency of blood group O less in patients suffering from cancer of the stomach than in the general population of the locality in which they live." Blood group O has been reported to be strikingly high, and the other three blood groups increasingly low, in patients suffering from peptic ulcer.2 Studies have revealed an inverse relationship between the frequencies of blood groups O and A in patients with gastric and duodenal lesions.3 An increased frequency of blood group A in diabetes mellitus has been reported,4 and blood group A has been shown in excess in children dying under two years of age from bronchopneumonia.5 Instances of toxemia of pregnancy, as compared with the nontoxemic patients, showed a significant increase of women of blood group O.5 On the other hand, carcinomas of the colon, rectum, breast, bronchus and lung do not appear to differ from the general population in the incidence of ABO groups.2, 6

Advantages of belonging to a specific member of the ABO groups are therefore suggested. The potentialities of this kind of information in a preventive medical program are evident. For these reasons we decided to undertake a study of the ABO blood groups in du Pont Company employees whose blood types were available in their medical records.

Four company locations having a combined population of 12,904 employees provided usable data. Among the various diseases prevalent in this population, only two—peptic ulcer and hypertension—appeared in sufficient numbers for adequate statistical analysis. There were 298 employees with a history of peptic ulcer and 508 with hypertension. The diagnosis of peptic ulcer was established by gastrointestinal x-ray series and history. Hypertension was diagnosed on the basis of blood pressure readings taken on two successive annual physical examinations. An employee was classified as hypertensive if both readings showed the systolic pressure to be 150 or greater and the diastolic pressure to be 95 or greater.

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TABLE 1

Blood Group Distributions, in Percentages, in Four Company Locations and in 141,774 Whites in the United States Who Donated Blood to the American Red Cross, 1948–49

Blood		Du Pont Employees						
Group	Location I	Location II	Location III	Location IV	Total	Estimate (Red Cross Blood Donors		
O A B AB	45.8 41.3 9.7 3.2	40.4 39.5 15.4 4.7	45.3 41.4 10.4 2.9	43.9 41.6 10.8 3.7	44.5 41.1 10.9 3.5	45.6 40.8 10.0 3.7		
	100.0	100.0	100.0	100.0	100.0	100.1		

TABLE 2

Blood Group Distribution: Peptic Ulcers and Control

Location			0	A	В	AB	Total
I	Number	Ulcer Control	60 2769	46 2508	17 585	5 189	128 605
		Total	2829	2554	602	194	6179
	Per cent	Ulcer Control	46.9 45.8	35.9 41.5	13.3 9.7	3.9 3.0	100.0
	Number	Ulcer Control	9 719	6 705	3 275	2 83	1782
H		Total	728	711	278	85	180
	Per cent	Ulcer Control	45.0 40.4	30.0 39.6	15.0 15.4	10.0 4.6	100.0
	Number	Ulcer Control	36 934	27 859	4 219	1 62	207-
III		Total	970	886	223	63	214
	Per cent	Ulcer Control	53.0 45.0	39.7 41.4	5.8 10.6	1.5 3.0	100.0
	Number	Ulcer Control	42 1179	29 1129	8 292	3 99	8 269
IV		Total	1221	1158	300	102	278
	Per cent	Ulcer Control	51.2 43.7	35.4 41.8	9.8 10.8	3.6 3.7	100.0
	Number	Ulcer Control	147 -5601	108 5201	32 1371	11 433	298 12,600
Total		Total	5748	5309	1403	444	12,90
	Per cent	Ulcer Control	49.3 44.4	36.2 41.3	10.8	3.7 3.4	100.0

The control group for each location comprised all employees who showed no history or evidence of the disease studied. Comparisons of the distribution of the ABO blood groups among the four locations, with an estimate of the distribution in the total population of the United States, are shown in table 1.7 With the exception of location II, which shows a pronounced decrease in O and increase in B when compared to the other locations, the distribution of the blood group among the company employees is very close to the estimate in the United States.

FINDINGS

The distribution of the blood groups among subjects of the disease and the control groups for each location are shown in table 2 for peptic ulcer and in table 3 for hypertension.

Table 3
Blood Group Distributions: Hypertension and Control

Location			0	A	В	AB	Total
1	Number	Hypertension Control	130 2699	135 2419	31 571	7 187	30. 5870
		Total	2829	2554	602	194	6179
	Per cent	Hypertension Control	42.9 45.9	44.6 41.2	10.2 9.7	2.3 3.2	100.0
Nı	Number	Hypertension Control	27 701	41 670	13 265	8 77	1713
H		Total	728	711	278	85	1802
	Per cent	Hypertension Control	30.3 40.9	46.1 39.1	14.6 15.5	9.0 4.5	100.0
	Number	Hypertension Control	34 936	27 859	6 217	61	2073
III		Total	970	886	223	63	2142
	Per cent	Hypertension Control	49.3 45.2	39.1 41.4	8.7 10.5	2.9	100.0
	Number	Hypertension Control	19 1202	21 1137	3 297	4 98	2734 2734
IV		Total	1221	1158	300	102	2781
	Per cent	Hypertension Control	40.4 44.0	44.7 41.6	6.4 10.9	8.5 3.5	100.0
	Number	Hypertension Control	210 5538 -	224 5085	53 1350	21 423	508 12,396
Total		Total	5748	5309	1403	444	12,904
	Per cent	Hypertension Control	41.3	44.1 41.0	10.4 10.9	4.2 3.4	100.0

Table 4
Relation of Peptic Ulcers to Blood Groups O and A

Location		0	A	Total	0 0+A	Difference (Ulcers- Control)	Chi-Square (1 d.f.)
I Ulcers Control	60 2769	46 2508	106 5277	.5660 .5247	+.0413	0.711	
	Total 2829 2	2554	5383	3 .5255		(P=.40	
II	Ulcers Control	9 719	6 705	15 1424	.6000 .5049	+.0951	0.539 (P=.46)
	Total	728	711	1439	.5059		
Ш	III Ulcers Control	36 934	27 859	63 1793	.5714 .5209	+.0505	0.622 (P = .43)
	Total	970	886	1856	.5226		
IV	Ulcers Control	42 1179	29 1129	71 2308	.5916 .5108	+.0808	1.796
	Total	1221	1158	2379	.5132		(P=.18)
Total Ulcers Control		147 5601	108 5201	255 .5765 10,802 .5185 +.0586	÷.0580	3.352	
	Total	5748	5309	11,057	.5199		(P = .07)

Combined weighted mean difference: +.0577 (P=.07)

When the totals only are examined, it is seen that the ulcer patients show an increase in type O and a decrease in type A. The difference from the controls in both blood groups is about 5%. Differences in the B and AB groups are very small.

Among hypertensives there appears to be a reverse tendency, that is, a decrease in O and an increase in A, but the differences between the disease and control groups are smaller: 3.4% in O and 3.1% in A. As in the peptic ulcer series, differences in the B and AB groups are small.

Further analysis of the data will be confined to the O and A groups for the following reasons: (1) The data indicate that the major differences between the diseased and control employees occur in these blood groups. (2) The inclusion of the B and AB groups in the statistical analysis will tend to dilute the strength of the relationship between the disease and the O and A groups. (3) There is a comparatively small number of diseased persons in the study who have B or AB blood. (4) The study of two blood groups reduces the data to a series of 2 by 2 contingency tables, and thus broadens the scope of the statistical analysis, in the manner described below.

Breakdown of the O and A blood groups by location, and the presence or absence of the disease studied, are shown in tables 4 and 5. Adding the data from each location to perform a combined test of significance is advisable

Table 5
Relation of Hypertension to Blood Groups O and A

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Location		0	A	Total	$\frac{O}{O+A}$	Difference (Hyp Control)	Chi-Square (1 d.f.)
I Hypertension Control	130 2699	135 2419	265 5118	.4906 .5273	0367	1.368	
	Total 2829 2554	2554	5383	.5255		(P = .24)	
II	Hypertension Control	27 701	41 670	68 1371	.3971 .5113	1142	3,383 (P=.07)
	Total	728	711	1439	.5059		
III Hypertension Control Total		34 936	27 859	61 1795	.5574 .5214	+.0360	0.305 (P=.58
	Total	970	886	1856	.5226		
IV	Hypertension Control	19 1202	21 1137	40 2339	.4750 .5139	0389	0.238 (P=.63)
	Total	1221	1158	2379	.5132		(103)
Total Hypertensic Control	Hypertension Control	210 5538	224 5085	434 10,623	.4839 .5213	0374	2.343 (P = 13)
	Total	5748	5309	11,057	.5199		(P = .13)

Combined weighted mean difference: -.0391 (P=.11)

only when the proportions of a specific blood type in the total population of each location are the same or nearly the same. This condition is fairly well met in this set of data, but to provide a more valid test of significance, a method of combining 2 by 2 contingency tables described by Cochran 8 was used. This method involves the computation of a weighted mean difference, and dividing it by its standard error to obtain a test criterion. The weighting of the difference in proportions in each location takes into account the sample size of the disease and the control series.

Table 4 shows the proportion of persons with O blood (O/O + A) among peptic ulcer patients and controls in each location. The unweighted pooled difference (peptic ulcer minus controls) is + .0580, while the combined weighted mean difference is + .0577, a negligible disparity. Testing the null hypothesis that the latter difference comes from a population whose mean is zero, we obtain P = .07. When the pooled data are tested by chisquare, P is again equal to .07. Although this probability falls somewhat short of the conventional .05 level of significance, the data do show a distinct tendency for an excess of group O blood to occur among persons with peptic ulcer, particularly in view of the fact that the difference is positive in each location. One should not be misled by the small values of chi-square in locations I, II and III. They merely reflect, in this case, the inability to detect a statistical relationship with the small samples of peptic ulcer patients

in each location. When the data are combined, the consistent positive differences are taken into account and a stronger statistical association is indicated.

These findings are in substantial agreement with those of other investigators. Buchanan and Higley (cited by Koster et al.³), Aird et al.² and Clarke ⁴ found an increased proportion of group O and a reduced proportion of group A among the peptic ulcer cases they observed. Aird et al. performed an analysis similar to the one presented here on 2,712 peptic ulcer cases, from three different areas, with O and A blood only. They obtained a weighed mean difference of + .0805, compared with + .0577 in this study.

The data on employees with hypertension, presented in table 5, do not indicate a completely clear or consistent pattern. However, there appears to be some evidence that a person with A blood is more likely to have hypertension than is a person with O blood. In a comparison of the proportion of persons with O blood among hypertensives and among the controls, negative differences are seen in three out of the four locations. One of these, Location II, shows a difference of — .1142 (chi-square = 3.383, P = .07). The combined weighted mean difference is — .0391. This difference, however, can be attributed to chance (P = .11). The inconsistency in the data occurs in location III, where the difference is positive and equal to .0360. Nevertheless, the appearance of negative differences in three out of four locations, and the pronounced difference in Location II, do indicate that further study of the relation of the ABO blood groups to hypertension is warranted.

SUMMARY

Reports in the medical literature on significant relationships between ABO blood groups and certain diseases have led the authors to study the distribution of the blood groups among 298 persons with a history of peptic ulcers, and 508 cases of hypertension, among 12,904 employees in four locations of the du Pont Company.

It was found that the cases of peptic ulcer showed an increased frequency of O blood and a reduced frequency of A blood of about 5% when compared with a control group. This relationship is consistent with, but not so great

as, that obtained by other investigators.

The findings among hypertensives were inconclusive, but did suggest the possibility that persons with type A blood have a slightly greater chance of developing hypertension than have those with type O blood. Additional data are needed to clarify the nature and extent of this relationship.

Consideration might be given to these findings in a preventive medical program.

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SUMMARIO IN INTERLINGUA

Iste investigation esseva interprendite pro explorar additionalmente le relationes reportate in le litteratura medical inter le gruppos sanguinee ABO e certe morbos. Un numero de studios ha monstrate un augmentate frequentia de sanguine del gruppo A in diabeticos e in personas con cancere del stomacho. Augmentate frequentias del gruppo O ha essite notate in personas con ulcere peptic e in casos de toxemia de pregnantia.

Le datos usate in le presente studio es colligite ab 298 casos de ulcere peptic e 508 casos de hypertension inter 12,904 empleatos in quatro brancas del Compania du

In omne le quatro brancas, le proportion de personas con sanguine de gruppo O es plus alte inter le casos de ulcere que inter individuos sin historia de ulcere peptic. Le differentia del incidentia de sanguine del gruppo O inter le duo categorias de empleatos amonta a circa 5 pro cento. Iste relation se accorda con constatationes

per altere investigatores, sed illo es minus marcate.

Ben que le datos con respecto a hypertension variava considerabilemente inter le quatro brancas, illos indica le possibilitate que un persona con sanguine del gruppo A curre un plus grande risco de disveloppar hypertension que personas con altere gruppos de sanguine. In tres del quatro brancas il esseva trovate que le hypertensivos include plus basse procentages de sanguine del gruppo O e plus alte procentages de sanguine del gruppo A que le non-hypertensivos. Le magnitude de iste differentia in le tres brancas varia inter 3,7 e 11,4 pro cento. In le serie total, le frequentia de sanguine del gruppo A inter hypertensivos excede le frequentia de sanguine del gruppo A inter non-hypertensivos per 3,7 pro cento. Tamen, iste differentia pote esser attribuite a variationes in le selection del subjectos. Datos additional es requirite pro clarificar le natura e le grado de iste relation.

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MOLECULAR DISEASES OF HEMOGLOBIN. I. IN-TRODUCTION AND INCIDENCE *

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HISTORICAL

THE discovery by Pauling, Itano, Singer and Wells 1 that normal and sickle cell hemoglobins have different electrophoretic mobilities provoked a great amount of thought and investigation concerning the molecular aberrations of hemoglobin. To the clinician as well as to the medical investigator, this discovery crystallized the concept that a molecular abnormality in a single substance might cause a sequence of events productive of serious disease states. For the clinical hematologist and the geneticist, the study of abnormal hemoglobins has provided a method of classifying inherited hemoglobin disorders which no other approach has equaled in simplicity and accuracy.

Prior to 1949 it was known only that differences existed between adults and fetal hemoglobin, but the newer methodology has uncovered at the present time seven other abnormal forms in addition to Hgb. S.

Notable contributions to the biochemical, laboratory and clinical aspects of the abnormal hemoglobins have been made by Itano,2 Pauling,3 Margolies,4 Leavell and MacIlwaine,5 and Smith and Conley.6 Chernoff 7 and Singer 8 have written excellent reviews of the subject.

BIOCHEMISTRY

Hemoglobin is composed of four heme molecules which are attached to a protein molecule, globin. The heme portion of the molecule and its attachment to the protein are the same throughout the vertebrate kingdom. The globin fraction exhibits species specificity, and therefore differs from one species to another. Although it is believed that the defect in the abnormal hemoglobin occurs in the globin fraction, the precise manner in which these abnormal hemoglobin molecules differ from each other is not yet clear. Inasmuch as molecular weights and amino acid compositions are very similar,9 it seems probable that alterations in the arrangement of the amino acids in the globin molecule produce different end groupings and different

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folding of the amino acid chains, thereby affecting the physiochemical characteristics of the entire hemoglobin moiety.

Nomenclature

The rapid advances in this field naturally led to some confusion in terminology, and in January, 1953, a symposium on hemoglobin abnormalities ¹⁰ adopted the following system of nomenclature: A for normal adult hemoglobin, F for fetal, S for sickle, and C and D for the other two abnormal pigments known at that time. ^{11, 12} As other new types of hemoglobin were detected they were to be assigned letters of the alphabet in the order of their discovery. Subsequently E ¹³ and G ¹⁴ were recognized in 1954, H and I ^{15, 16} in 1955, and J ²² in 1956.

In the designation of syndromes involving more than one hemoglobin it is now the practice to list the major component first.⁷

CLINICAL SYNDROMES

The hemoglobin disorders may be subdivided into the *traits* and the *disease states*. In the traits there is a combination of A or normal hemoglobin with any one of the abnormal hemoglobins, e.g., in sickle cell trait Hgbs. A and S are present while Hgbs. A and C are found in C trait. In patients with the trait the majority of hemoglobin is A type. No pathologic states are associated with such traits except under unusual circumstances.¹⁷ On the other hand, Hgb. A is not present in the disease states, and some evidence of disturbed physiology is invariably present. These diseases can be pure or homozygous (S-S or sickle cell disease, C-C or pure C disease), or they can be mixed or double heterozygous (S-C disease, S-D disease, etc.). In these conditions it is not unusual to have small amounts of Hgb. F present in the erythrocytes, the reason for this apparently being related to genetic aspects (see below).

Sickling of red cells (drepanocytosis) is found only if Hgb. S is present, while target cells (leptocytosis) may be found with the other abnormal forms of hemoglobin, especially C.

GENETIC ASPECTS

Although it is known that these abnormalities are hereditary, the finer genetic aspects are still largely in the field of speculation. It is known that sickle cell anemia results only when both parents contribute abnormal genes; therefore, both parents must have either the trait or the disease state. Since the S trait results only when one parent contributes the abnormal gene, the trait cannot result if both parents have sickle cell anemia. The assumption that the determinates for pathologic hemoglobin types are alleles of the genes for Hgb. A still provides the most satisfactory explanation of the basic genetic features of these diseases, ¹⁸ and since the expressivity (the degree to

which a particular gene becomes manifest) of the abnormal gene varies markedly from individual to individual, the influence of modifying genes has also been postulated.¹⁹

The presence of Hgb. F in irregular amounts in homozygous and double heterozygous conditions presents another perplexing problem, and an attempt at clarification has led to the following postulates: 8

- 1. Hgb. F production is also controlled by genes which are not alleles for those of A.
- 2. The activities of the F genes are almost completely suppressed by the genes for A in the post-infancy period.
- This suppression becomes less complete if certain pathologic gene combinations exist which result in hemoglobin and/or red cell structure abnormalities.

Hgb. A appears to have a greater expressivity than the other hemoglobin types, and when it appears with an abnormal hemoglobin (trait), more than 50% of the total will be A type. Hgb. C is slightly dominant over hemoglobin S. Under the third postulate it would appear that C, D and E suppress F to a lesser extent than A, whereas S is the least potent inhibitor. The degree of suppression of F production seems to be determined by the most potent inhibitor present in the hemoglobin combination. For this reason no F is seen in the trait states, while significant amounts are seen in sickle cell anemia.

The thalassemia factor is associated with increased expressivity of S, C, E and F, and may in turn inhibit normal A formation.

TECHNICS FOR STUDY

The dissimilarities of human hemoglobin types have been uncovered by the application of methods generally used for the study of proteins: electrophoresis, alkali denaturation, solubility, spectroscopy, immunologic behavior, amino-acid composition, and other physiochemical methods. The simple, quick and inexpensive filter paper electrophoresis separates all but one of the hemoglobins commonly found in the United States. Hemoglobins A, F and G have essentially the same electrophoretic mobilities, and hemoglobins S and D move at the same rate. Of these, G and D are very rare, and F may be detected by a simple alkali denaturation determination. A diagrammatic presentation of the mobilities of the various hemoglobins on filter paper electrophoresis is seen in figure 1. Hemoglobins H, I and J move more rapidly than adult hemoglobin; F and G move at about the same rate, and the rest move more slowly.

INCIDENCE

In the United States the great majority of aberrations of hemoglobin involve S, C and thalassemic abnormalities in decreasing frequency, whereas

those of E, G and H are extremely rare. Using paper electrophoresis, Smith and Conley ²⁰ and Schneider ²¹ have studied the incidence of abnormal hemoglobins in Baltimore and Galveston, respectively. We have employed a similar technic in evaluating the incidence of these aberrations in patients from both the in-patient and the out-patient service of Jefferson Davis Hospital, a city-county hospital serving the indigent population of Houston and Harris County and affiliated with Baylor University College of Medicine.



Fig. 1. Electrophoretic mobility of the various hemoglobins in barbital buffer at pH 8.6.

METHODS

The electrophoresis cells used were quite similar to those described by Slater and Kunkel.²⁶ Electrophoresis was carried out between glass plates using Whatman No. 3 filter paper and a Heathkit PS-2 power supply. The barbital buffer, pH 8.6, was prepared by dissolving 41.2 gm. of sodium barbital and 7.36 gm. of di-ethyl barbituric acid in 4 liters of distilled water. Hemoglobin solutions were prepared from oxalated blood by lysing the erythrocytes in equal volumes of distilled water after previous separation of the cells from the serum. After lysis, two volumes of barbital buffer were added to give a final concentration of 3 to 9 gm.% hemoglobin. This solution was then centrifuged at 2500 RPM for 15 minutes.

Electrophoresis was performed on 0.01 ml. samples at 15 milliamperes (400 to 450 volts) for five hours at room temperature. The strips were dried for 15 minutes at 110° C. and then stained with bromphenol blue.

Under the conditions outlined, paper electrophoresis clearly delineates A, S and C hemoglobins, whereas F could not be separated unless the time of the electrophoresis were extended to eight to 10 hours, when F could be detected trailing just behind the normal hemoglobin. This is not, however, a dependable method for detection of F hemoglobin.

Important factors in obtaining good patterns are as follows:

- 1. Lyse the cells completely and obtain a proper dilution if good separation of the hemoglobin moieties is to be accomplished. Washing the cells with normal saline before hemolysis is not essential if the serum is separated and removed before adding distilled water.
- 2. The prevention of "spotting" at the point of application of the solution to the filter paper is aided by centrifuging the final dilution for at least 15 minutes at 2,500 RPM. A small amount of trailing often occurs but this can be disregarded.

TABLE 1

Series	Race	Number	A—S Sickle Trait		S—S Sickle Cell Anemia		s-c		C Trait A—C		C disease	
			#	%	#	70	#	%	#	1 %	#	%
Jefferson Davis	White Negro	350 400	0 36	0 9.0	0 5	0 1.3	0	0.25	0	0	0	0.25
Johns Hopkins ²⁰	White Negro	500 500	0 36	0 7.2	0 5	0 1.0	0	0 .2	0 9	0 1.8	0	0
John Sealy ²¹	White Negro	60 505	0 47	0 11.3	0	0	0	0	0 15	0 3.0	0	0
Total	White Negro	910 1405	0 119	0 8.4	0 10	0 .7	0 2	0 .15	0 30	0 2.1	0	0.07

3. There is some tendency for the samples placed near the center of the apparatus to travel further than the ones on the periphery. For this reason a normal sample was placed in the center and on each edge of the strip. Whenever doubt existed that a hemoglobin component was normal or abnormal in its mobility, some of the questionable hemoglobin solution was mixed with a known normal sample and the pattern of the mixture studied after electrophoresis. In this series, suspected abnormals were also run with a known abnormal, usually A-S (sickle trait), a procedure which facilitated diagnosis.

In practice, the hemoglobins seldom move as sharply as is indicated in figure 1, due in the main to their trailing tendencies. In addition, when two hemoglobins coexist in the same blood specimen they possess a mutual attraction which alters their respective positions slightly.²⁸

RESULTS

The results obtained in this survey are listed in table 1 and are compared with those obtained by Smith and Conley from the clinic population at The Johns Hopkins Hospital, and by Schneider from the blood bank at John Sealy Hospital. The present study (Jefferson Davis Hospital) and the study at the Johns Hopkins, representing the incidence in general hospital populations, agree quite well. The study by Schneider differs in that persons with overt hemolytic disease or anemia are not permitted to donate blood; consequently, persons with known hemoglobin disease would not appear in a series based on blood bank donors. Persons with asymptomatic trait abnormalities, on the other hand, would be included in such a survey, and Schneider's statistics provide a good indication of the incidence of trait abnormalities in a population considered to be normal.

Of 910 white persons screened by electrophoresis in all three series, no abnormal hemoglobins were found. In the 1,405 Negroes there was an incidence of 11.4% of abnormal hemoglobins as detected by electrophoresis. S hemoglobin was present in 9.4% and C in 2.2% of the Negroes. Only one case of homozygous C disease was detected in the three series.

The sickle trait was found in 7.2% to 11.3% in these three series, with a mean of 8.4%, thereby providing essential agreement of trait incidence between electrophoretic technics and those based on the findings of in vitro sickling. The incidence of sickle cell anemia has been estimated at 0.22% by Neel and Schull. The study at Jefferson Davis Hospital indicates an incidence of 1.3% and a ratio of trait to anemia of 7 to 1. If the incidence in the two general hospital populations is combined, the incidence of sickle cell anemia is 1.1%, that of trait is 8.0%, and the ratio is 7.2:1. The figures from all three series combined agree quite well with the old maxim that approximately 10% of the Negro population has sickle cells in the peripheral blood and that 10% of this group has sickle cell anemia.

Conclusions

- 1. The basic factors in molecular diseases of hemoglobin are reviewed.
- 2. Filter paper electrophoresis is the best single method for detection of these abnormalities. This method will separate all but combinations of A, F and G, and combinations of S and D.
- 3. The most common abnormal hemoglobin is S, while C is encountered less frequently.
- 4. The syndromes encountered are: trait, homozygous disease, and double heterozygous disease.
- The incidence of molecular disease of hemoglobin in Negroes is about 11.5%.
- 6. No cases were found in 910 white persons reported in three series using filter paper electrophoresis.

SUMMARIO IN INTERLINGUA

Le discoperta que hemoglobina normal e hemoglobina de cellulas falciforme manifesta differente mobilitates electrophoretic ha aperite nove possibilitates diagnostic e nove methodologias investigatori in le campo del hereditabile disordines hemoglobinic. Depost 1949, octo hemoglobinas anormal ha essite describite, i.e. hemoglobinas C, D, E, G, H, I, J, e S. In illos, le anormalitate se trova in le fraction de globina. Ab le puncto de vista clinic, le disordines es dividite in tractos e statos pathologic. In le tractos, hemoglobina A, i.e. hemoglobina normal, es trovate insimul con un del hemoglobinas anormal, e-como regula general-nulle symptomas es presente. In le statos pathologic, il pote haber homozygotic o duple heterozygotic combinationes de hemoglobinas anormal. Hemoglobina A es absente, hemoglobina F, i.e. hemoglobina fetal, es presente in quantitates irregular, e certe signos de un disturbate physiologia es evidente. Le hereditage seque leges mendelian de un gen dominante, sed le detaliate aspectos genetic non es clar. Il pare que hemoglobina A possede un plus grande expressivitate que le altere typos de hemoglobina.

Electrophorese a papiro-filtro es le melior technica individual pro le detection del varie hemoglobinas. A, F, e G ha essentialmente le mesme mobilitate, e S e D se move al mesme rapiditate. Le altere cinque hemoglobinas se move a differente velocitates. De G es multo rar, e F pote esser detegite per un simple determination de disnaturation alcalin. In le Statos Unite, S, C, e thalassemia constitue le grande majoritate del anormalitates incontrate. In 400 patientes negre, studiate al Hospital Jefferson Davis a Houston in Texas per le methodo del electrophorese a papirofiltro, le incidentia del tracto S esseva 9 pro cento; de anemia a cellulas falciforme, 1,3 pro cento; de morbo S-C, 0,25 pro cento; del tracto C, 1,5 pro cento; e de homozygotic morbo C, 0,25 pro cento. Iste cifras monstra un satis bon accordo con illos obtenite per Smith e Conley in un serie studiate per illes al Hospital Johns Hopkins a Baltimore in Maryland. Schneider, qui laborava a Galveston in Texas con donatores de sanguine (lo que elimina le statos pathologic del hemoglobinas anormal), trovava un incidentia de 11,3 pro cento pro le tracto de S e de 3 pro cento pro le tracto de C. Nulle altere formas de hemoglobina anormal esseva trovate inter le 1.405 patientes negre in le tres series combinate, e nulle hemoglobinas anormal esseva trovate inter le 960 patientes blanc.

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FACTITIOUS FEVER*

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THE problem of elucidating the etiology of fever is one of the most fascinating and challenging that confronts the physician. It is of course well recognized that fever can be a prominent manifestation of many diseases of widely diversified etiology, and that the diagnostic possibilities in any given case may be legion. Furthermore, because body temperature is routinely recorded in clinical practice and considered to be an "objective" physical finding, its reliability is rarely questioned. Thus, while a definitive diagnosis is not always established in febrile illnesses, so-called "F.U.O.'s," the question of whether a patient actually has fever is seldom seriously raised. Obviously, before embarking upon a prolonged, tedious and expensive search for the cause of fever, one should be sure that the elevation in temperature is not a spurious phenomenon. It is the purpose of this report to describe cases of "fever of unknown origin" observed by the authors or their associates in which there is reason to believe that abnormally high temperatures were recorded by deliberate fraud. These patients were observed at the Grace-New Haven and The Johns Hopkins Hospitals, and represent a selected group gathered by personal communication rather than systematic review of hospital records. For this reason, no conclusion as to the incidence of spurious fever can be drawn from these cases.

The essential data for each case are summarized in table 1. The patients can be divided in two groups: those in whom fever was the presenting complaint (cases 1, 1a, 2–7), and those whose difficulties were not manifested primarily by fever, although elevation of temperature was an incidental "objective" finding (cases 8–13). Twelve of the 14 were females whose mean age was 32 years. Five of these 12 were nurses. Only two of the patients had temperatures in the hyperpyrexic range (greater than 106° F.). This contrasts with many previously described cases of spurious hyperpyrexia which have been reported because of the abnormally high fevers recorded. The duration of fever varied widely in these patients, but was at least two weeks in every case. In cases 8 and 9 the episodes reported in detail lasted only 10 days, but both patients had had previous bouts of "febrile" illness of the same type. Multiple complaints were common, and

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Table 1 Clinical Data in 14 Cases of Spurious Fever

Case	Sex	Age	Occupation	Temp. Range °F.	Dura- tion of Fever	Chief Complaint	Proof of Fraudu- lent Fever	Other Manifesta- tions	Previous Record of Factitious Disease
1	F	23	Housewife	99-103.8	3 wks.	Fever	Yes	Abd. pain	None
1a	F	29	Nursing aide	98.6-102	3 mos.	Fever	Yes	Abd. pain	None
1a 2	F	18	Student	99-103.4	2 wks.	Fever	No		None
3	F	21	-	99.2-105.2	4 mos.	Fever	Yes	Hematuria	Yes
3 4	F	25		98-102	2 wks.	Fever	Yes	Dermatitis; sto- matitis	Yes
5	F	59	Housewife	100-101.2	2 wks.	None*	Yes		None
5 6 7	F	23	-	99-109	2 wks.	Fever	Yes	Urinary retention	Yes
7	F	22	Nurse	98,6-104,8	2 wks.	Fever	Yes	Nausea, vomiting	No
8	M	38	-	98-106,6	10 days	"Blacking- out"	Yes	Left hemianesthesia	Yes
9	M	44	_	98.6-103.2	10 days	Chest pain	Yes		Yes
10	F	34	Nurse	98.6-101.6	3 wks.	Weakness	No	Wt. loss	Probable
11	F	51	Housewife	98-101.4	3 wks.	Nervousness	No	Thyrotoxicosis	No
12	F	41	Nurse	98-102	3 wks.	Addison's disease	No	Hypoglycemia	Yes
13	F	37	Housewife	97-102	6 mos.	Pain in legs	Yes	Purpura	No

* Temperature recorded falsely by private nurse.

other illnesses, at least some of which were factitious, were present in 10 patients, although, as mentioned, factitious syndromes other than fever were the chief complaints in only six instances. Seven patients had well documented records of previous admissions to other institutions for fraudulent symptoms.

CASE REPORTS

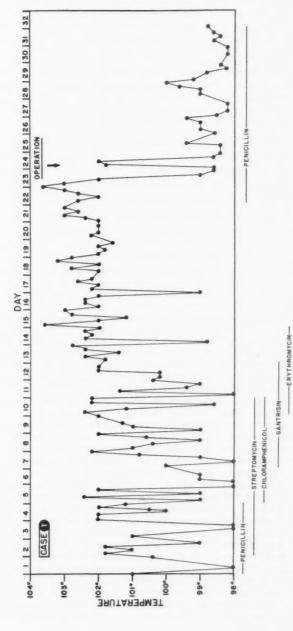
Case 1 (figure 1). A 23 old white married female was hospitalized because of fever and lower abdominal pain.

Three weeks previously she had undergone uterine curettage for a spontaneous, incomplete abortion. The postoperative course was uncomplicated and she had been discharged without symptoms. For five days she had noted chilly sensations, fever and lower abdominal pain. Persistence of these symptoms led to readmission to the hospital

Physical Examination: Temperature, 100° F.; pulse, 100. There was some tenderness in the right lower quadrant, and the uterus was enlarged, soft and tender. There was moderate vaginal bleeding. The remainder of the examination was not remarkable.

Laboratory Data: Red blood cells, 3.7 million per cu. mm.; hemoglobin, 11.0 gm.; white blood cells, 7,000, with a normal differential. Five additional leukocyte counts were normal. The initial urine was normal except for the presence of many white cells; a catheterized urine, however, was sterile on culture. Seven blood cultures were sterile.

Hospital Course: The patient was treated with a variety of antibiotics, including penicillin, streptomycin, chloramphenicol, Gantrisin and erythromycin (figure 1), without appreciable effect on her fever, which continued to range between 102° and 104° F. The working diagnosis was postabortal sepsis and pelvic thrombophlebitis. Because of the appearance of tenderness in the left lower quadrant and left femoral triangle, the process was thought to be spreading and an exploratory laparotomy was performed. Operation revealed a slightly enlarged, soft uterus; the ovaries, tubes and the iliac and ovarian veins were entirely normal. Several



Fr. 1. A 23 year old housewife was hospitalized for fever several weeks after an incomplete abortion. The diagnosis of pelvic thrombophlebitis was made, but exploratory laparotomy did not substantiate this impression. Postoperatively the patient admitted that the temperature elevations had been produced by fraud.

ovarian veins were ligated; histologic sections from these vessels and from a rectus muscle were normal. The patient's postoperative course was benign, the temperature remained entirely normal, and she was discharged 10 days after the surgical procedure.

Postoperatively, it was learned from the patient's roommate that the patient had taken her own temperatures and had admitted that she had been deliberately shaking the thermometer upwards. The absence of definite physical signs, normal laboratory data, and findings at operation, coupled with the patient's good general condition throughout the entire illness, made it seem altogether probable that the fever had indeed been produced by fraudulent means. In view of the prompt subsidence of fever postoperatively, the private physician in charge of the case felt that there was little to be gained by exploring the matter further and the patient was discharged.

A relatively benign illness in this patient apparently led to an acute episode of disturbed behavior characterized by a "febrile" illness which reached its climax in a major operative procedure. It is conceivable that the loss of the fetus constituted a sufficiently severe emotional trauma to act as a trigger-mechanism. There is no previous history of a major psychiatric disturbance in this patient, and no follow-up is available.

Case 1a. A 29 year old Negro nursing aide was hospitalized for recurrent fever. At the age of seven she was found to have pulmonary tuberculosis, which subsided on bed-rest, although an area of fibrosis remained in the left upper lung field. This lesion was followed at regular intervals by x-ray, and had shown no change for many years. In 1954 she had become pregnant for the first time, and extensive studies, including examination and culture of gastric washings, had shown no evidence of active tuberculosis.

She entered the hospital for a second pregnancy in 1956 and delivered a full term normal infant. Because of fever with daily spikes to 102° F. during the postpartum period, she underwent extensive studies aimed at detecting pelvic tuberculosis or reactivation of the pulmonary lesion. Hemogram, sedimentation rate and numerous bacteriologic studies showed no abnormality. A therapeutic trial of Gantrisin and erythromycin did not influence the fever, and it was finally decided to treat the patient with isoniazid. There was no defervescence, and the drug was discontinued on the advice of a medical consultant. The patient was asymptomatic, and on the eighteenth day after delivery became afebrile and was discharged shortly thereafter.

Three weeks later she was readmitted to the obstetric service complaining of fever, said to occur at 8 a.m. and 4 p.m. daily. There were no other symptoms. Physical examination and laboratory data were entirely normal. On several occasions the patient's temperature was checked within a few minutes after reported elevations, and invariably the thermometer registered within normal limits when a nurse remained with the patient. After several such checks the patient reported no more elevations and was discharged without having been questioned about trickery or fraud.

Several weeks later she reported to the medical clinic that fever had recurred. She complained of no other symptoms and underwent numerous tests as an out-patient, including blood cultures, another series of gastric washings for tubercle bacilli, and an L.E. cell test. An endometrial biopsy was normal, and the patient was finally readmitted to the hospital. On the day of admission, immediately after the patient had returned a thermometer registering a rectal temperature of 103.2° F. to the nurse, the intern on the ward held another thermometer in the patient's rectum for five minutes. The true reading was 98.8° F., and additional oral and rectal temperatures recorded during the next several hours were entirely normal. When the patient was confronted with the evidence of her deception she promptly left the hospital, and no follow-up is available.

This patient took advantage of her knowledge of hospital routine to falsify her temperature for about three months. The history of tuberculosis was also helpful in making the fever appear genuine, and deterred most of the attending physicians from considering the diagnosis of factitious fever. As in case 1, the onset of fever during the postpartum period in this patient raised the possibility of the complication of persistent low grade pelvic thrombophlebitis, although in both cases positive evidence for this disease was scanty.

Case 2 (figure 2). An 18 year old student nurse was admitted to the hospital because of intermittent fever of several weeks' duration. The history was not detailed enough to be of aid; and physical examination and laboratory studies were normal. The diagnosis remained obscure until the patient was seen by a medical consultant, who noted a striking discrepancy between pulse rate and body temperature, and suggested that the fever might be fraudulent. When the patient was confronted with the possibility that she might be falsifying her temperature chart, she was obviously embarrassed and uncomfortable but denied the accusation. Immediately thereafter, however, she became afebrile and the temperature remained within normal limits until she was discharged several days later. Her motive for falsely elevating the temperature and the exact means by which this was accomplished were never established.

Unfortunately, there is little background information available in this case of malingering by a student nurse. Inspection of the temperature curve, which is characterized by lack of the normal diurnal variation, several unusual quotidian spikes, and poor correlation between pulse and temperature, raised the question of falsely produced pyrexia.

Case 3 (figure 3). A 21 year old female was hospitalized in 1936 for repair of a pilonidal sinus. There was a history of an episode of jaundice four years prior to entry, an operative procedure for ptosis of the right kidney three years before admission, and an operation for a pilonidal cyst two years previously. She was also said to have had an attack of bilateral pyelitis the year prior to admission, which was successfully treated with numerous bladder irrigations.

Physical examination was normal. Laboratory examinations, including hemogram, urinalysis, blood cultures and cultures of urine taken from each kidney pelvis, showed no abnormality. Intravenous and retrograde pyelograms, barium enema and gall-bladder series produced no evidence of disease.

Hospital Course: Shortly after the patient's admission the pilonidal sinus was excised and she recovered satisfactorily. Prior to discharge, however, she had the first of several febrile episodes. There were no localizing signs. Concurrently with several of these temperature spikes, hematuria was noted in voided urine specimens. Catheterization on several occasions, however, failed to confirm the presence of blood. Many other diagnostic studies were carried out and hospitalization was prolonged for four months until the patient was found to have several thermometers in her possession, all of which registered higher than 104° F. She readily admitted having handed these thermometers to nurses after first elevating the temperatures artificially. All temperatures taken after the discovery of the thermometers were normal.

It is of interest that the patient was hospitalized again in 1955, 19 years after the reported episode, with multiple complaints, and the diagnosis of conversion hysteria was made.

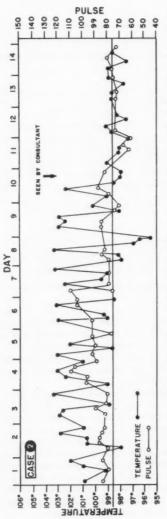


Fig. 2. An 18 year old student nurse ran a hectic febrile course without other manifestations. A consultant suggested that the fever might be spurious, and when the patient was confronted with this possibility the temperature curve returned to normal.

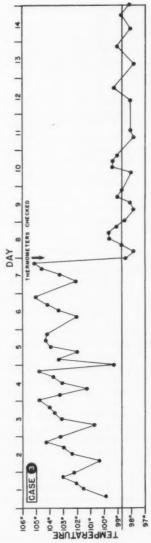


Fig. 3. A 21 year old female had several bouts of fever until discovery of a cache of thermometers with readings up to 104° F.

This patient manipulated thermometers and conveyed the impression that she was febrile for four months before the source of the recorded elevations of body temperature became evident. It is of interest that the fever usually reached its maximal levels at midnight or 4 a.m., a relatively unusual pattern in patients with organic disease. Hospitalization 19 years later confirmed the initial impression of hysteria with conversion symptoms.

Case 4. A 25 year old white female, separated from her husband, was transferred

from the Surgical Service for diagnosis of fever of unknown origin.

She had had numerous admissions to many hospitals for multiple complaints and operations. These included an appendectomy, removal of "tumors" from left arm and axilla, exploratory laparotomy for pyosalpinx, hysterectomy, a second abdominal exploration, rhinoplasty, and dilatation and uterine curettage on four occasions. She also stated unequivocally that she had had rheumatic fever, tuberculosis, and "trench mouth involving the lungs." She had been a patient at several mental hospitals and an inmate in the State Reformatory.

For two years prior to this admission she had been complaining of back pain, flank pain and dysuria, but numerous examinations, urinalyses and cultures were negative. For 10 days prior to entry she had complained of chills, fever, dysuria and cough. She was admitted to the Urological Service, where cystoscopy and pyelograms were normal, and then was transferred to the medical service for further study.

Physical Examination: Temperature, 99.2° F.; pulse, 100; respiration, 28; blood pressure, 120/70 mm. of Hg. The patient appeared tired but not ill. There were scattered macules over the neck and anterior chest, and several white papules and red macules over the oral mucosa. Examination of the heart, lungs, abdomen and

pelvis was within normal limits.

Laboratory Data: Hemogram was normal; sedimentation rate, 8 mm./hr. (Wintrobe). Urinalysis revealed 1 to 2 red blood cells and 2 to 8 white blood cells per high power field. Urine culture revealed Staphylococcus albus, but ureteral cultures obtained at pyelography were sterile. Cultures of the mouth, nose, throat and vagina grew out only normal flora. Blood cultures were sterile. Numerous agglutination studies, an L.E. cell test, and tuberculin skin test were negative. A chest film was normal.

Hospital Course: During the first few days in the hospital the patient's afternoon temperatures ranged from 101° to 102° F. There were no rigors or sweats. The presence of a nurse in the room resulted in disappearance of the fever spikes. The mouth and skin lesions were also thought to be factitious. Careful examination of the patient's record revealed several episodes of fever in the past which had probably been fraudulently induced. It was felt that the patient would not benefit from prolonged hospitalization, and as soon as it was ascertained that she had no significant organic disease she was discharged.

This woman had behavior problems of long standing and had spent much time in hospitals for illnesses which were probably factitious in origin. Her basic personality difficulties were, of course, not improved by the many physicians who catered to her complaints by performing surgical procedures on questionable indications, or by unnecessarily prolonging hospitalization. It is doubtful that she could have been benefited by psychiatric treatment.

Case 5. A 59 year old female was hospitalized for intermittent epigastric pain. Seven years prior to entry she had first noted episodes of intermittent epigastric pain radiating to both shoulders. The following year gall-stones were demonstrated

by x-ray, and a cholecystectomy was performed. She remained asymptomatic until four months prior to admission, when symptoms recurred and increased in severity. There had been no icterus, dark urine, acholic stools, chills, fever or weight loss.

Physical Examination: The patient appeared healthy. Vital signs were normal. There was no icterus or spider angiomata. Other than a well-healed right upper quadrant scar, the examination was entirely within normal limits.

Laboratory Data: Serologic test for syphilis, hemogram, sedimentation rate, urinalysis, nonprotein nitrogen, total protein with A/G ratio, bilirubin, bromsulphalein, amylase and blood sugar were normal. Serum alkaline phosphatase was 9.7 and 9.2 Bodansky units (normal, 5.6). X-rays of the upper gastrointestinal tract and kidneys were normal. Chest film revealed some elevation of the right diaphragm

and an old pleural reaction at the right base.

Hospital Course: Early in her hospital course the patient had a typical attack of pain, during which her bilirubin rose from 1.8 to 2.3 mg.% within six hours. This substantiated the initial impression of biliary tract disease and the patient was therefore subjected to laparotomy. A small remnant of gall-bladder was found; although there were no stones, the common duct was markedly dilated. Post-operatively the patient did well, except for a mild wound infection for which she was given chloramphenicol. She continued, however, to run a low grade fever which could not be explained. Because of the elevated right diaphragm a subphrenic abscess was suspected, even in the absence of leukocytosis, but needle aspiration of the area failed to reveal the presence of pus. It was then suspected that the elevations in temperature might be fraudulent. Indeed, the patient's temperature readings were entirely normal when taken by the ward physicians. It was finally determined that the patient's private duty nurse was recording false elevations of temperature to prolong the patient's hospital stay and thus insure a comfortable income for herself.

This unfortunate patient was the victim of an unscrupulous private nurse who sought to prolong the patient's hospital stay by recording falsely elevated temperatures on the chart. While this is an unusual type of fraudulent fever, it should be kept in mind in investigating cases of this type.

Case 6. A 23 year old divorced white female was transferred to the Medical

Service because of suspected typhoid fever.

Four months before entry the patient had developed dull, throbbing headaches, followed by gross hematuria and oliguria. These symptoms subsided after two weeks without specific treatment. Six weeks before admission she had accidentally swallowed two pins, and shortly thereafter developed lower abdominal pain, nausea and vomiting. She was admitted to another hospital, where a laparotomy was performed and one pin was successfully extracted from the pyloric area. She recovered uneventfully. It was noted on one occasion, preoperatively, that there was an increase in temperature from 98.6° to 104.6° within four hours, without concomitant increase in pulse or other abnormal signs and symptoms.

One week before admission she suddenly developed headache, nausea, vomiting and right lower quadrant pain. Because of an episode of syncope just outside the door of the Accident Room, she was admitted to the Gynecological Service as an emergency. There were no abnormalities on examination. She ran a peculiar spiking

fever and required repeated catheterizations because of urinary retention.

Physical Examination: Temperature, 100.4° F.; pulse, 76; respirations, 42; blood pressure, 100/65 mm. of Hg. The patient was a well developed, well nourished white female in no distress; she was breathing rapidly, but there was no dyspnea, orthopnea or cyanosis. The only abnormalities were found on abdominal examination. The liver was palpable 2 cm. and the spleen 1 cm. below the costal margins, and there were

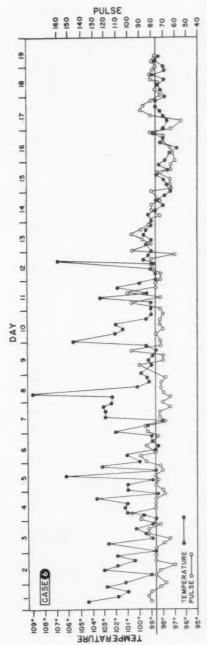


Fig. 4. A 21 year old woman had repeated bouts of urinary retention and marked hyperpyrexia up to 109° F. Simultaneous oral and rectal rectal

three well-healed abdominal scars. There was considerable right lower quadrant discomfort without spasm or rebound tenderness.

Laboratory Data: Serologic test for syphilis, negative. Hemogram, normal. White blood cells, 4,500, with a normal differential. Icterus index, 10; sedimentation rate, 8 mm./hr. (corrected). Several urinalyses were negative. Repeated blood cultures were sterile. Stool cultures grew no enteric pathogens, and urine cultures were negative. Bacterial agglutinations were negative, as were skin tests for trichinosis and tuberculosis. X-rays of stomach, small bowel and colon, and intravenous pyelograms were normal.

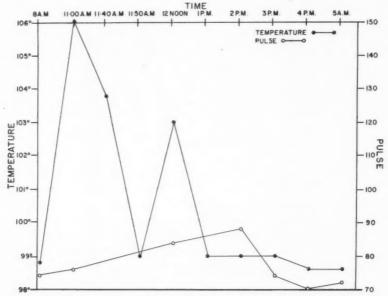


Fig. 5. Case 6. The decrease in temperature from 106.2° to 99° in a 20 minute period was not associated with tachycardia or diaphoresis. This discrepancy should lead to the strong suspicion of factitious fever.

Hospital Course: While the patient was on the Medical Service she ran a bizarre febrile course with spikes as high as 107° F. on several occasions (figure 4). There was one recorded episode of defervescence from 106° to 99° F. within 20 minutes (figure 5). In spite of the hectic temperature swings, the pulse was always slow and the patient did not look particularly ill.

Early in her course many diagnoses, including miliary tuberculosis, brucellosis, typhoidal tularemia and Salmonella suipestifer septicemia, were entertained. However, evidence for any of these was lacking, and it soon became obvious that the patient's fever was fraudulent. Simultaneous oral and rectal temperatures were taken; often there was wide disparity between the two readings, but the oral recording was always within normal limits.

The patient was seen by a psychiatric consultant, whose impression was hysteria. He felt the temperature to be factitious, and also noted that the patient was frigid and had certain homosexual tendencies. When the patient was confronted with the

discrepancy between her mouth and rectal temperatures she became quite indignant. However, she had no fever thereafter. The means by which these temperatures were produced was never determined. She was discharged afebrile on the eighteenth hospital day.

This patient's hyperpyrexia, and the urinary retention as well, were probably produced by trickery. The relative bradycardia led initially to consideration of typhoid fever. The technic used by the patient to produce the striking temperature spikes was probably manipulation of the thermometer by contraction of the anal sphincter. This method has been reported previously, ¹⁻⁸ and was used by at least one other patient in this group. Like most of the others, this woman proved to have deep-seated psychiatric difficulties.

Case 7 (figure 6). A 22 year old nurse was admitted to the hospital because of fever, nausea, vomiting and occipital headache of two days' duration.

Three years prior to admission she had become jaundiced and febrile, and had had pain in the right upper quadrant. A presumptive diagnosis of amebic hepatitis

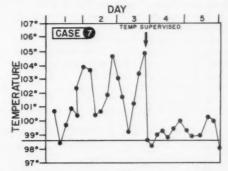


Fig. 6. This nurse was thought to have Charcot's intermittent fever until it was found that temperatures recorded by the physicians in attendance were invariably normal.

was made at another hospital, and she was treated for this disorder. When she failed to improve after six weeks of therapy, laparotomy was performed and liver biopsy was said to be normal. She recovered uneventfully over a period of three months.

She remained in good health until approximately three months prior to entry, when she had a two-day illness characterized by malaise, fatigue, headache, nausea and vomiting, and fever up to 102° F. She recovered spontaneously but had similar episodes two months and one month prior to admission. The latter illness was said to be associated with a true rigor lasting 20 minutes. Two days before admission she again noted symptoms of malaise, headache and fever to 104° F., and had a shaking chill. She was admitted to the infirmary, where physical examination was normal. It is of interest that temperature spikes occurred only around midnight and there was no objective evidence of temperature elevation, inasmuch as the patient was permitted to take her own temperature. Because of persistent headache, malaise and crampy abdominal pain she was hospitalized for study. There had been an 18 pound weight loss in the six months prior to admission, but no symptoms suggesting abnormality in the respiratory, gastrointestinal or genitourinary systems.

Physical Examination: The temperature was 102.4° F.; the remainder of the vital signs were normal. The patient appeared pale and wan but not acutely ill. Small, nontender lymph nodes in the posterior cervical chains and left axilla, and a well healed, slightly tender right upper quadrant scar constituted the only abnormal findings.

Laboratory Data: Urine, stool, hemogram and serology were within normal limits. Sedimentation rate was 7 mm./hr. (Wintrobe) corrected. Blood, nose and throat cultures were not remarkable. Tuberculin test was nonreactive. Immunologic studies for typhoid, paratyphoid, brucellosis, tularemia, infectious mononucleosis, primary atypical pneumonia and psittacosis were negative. Nonprotein nitrogen, total protein with A/G ratio, and liver function tests were normal. Chest x-ray was normal.

Hospital Course: On admission there were some nausea and malaise, which were treated symptomatically. The diagnosis of Charcot's intermittent fever secondary to incomplete biliary obstruction was initially entertained; however, several peculiar aspects of the temperature curve were noted. First, the febrile spikes usually occurred between 10 p.m. and midnight, and daytime temperatures were close to normal. Second, on one occasion the temperature dropped from 104.6° to 98.2° F. in 40 minutes, without concomitant change in pulse rate or the appearance of sweating. The latter temperature was obtained with the house officer in attendance, whereas the first was taken by the patient. Third, after the remarkably rapid defervescence just described, the temperature remained normal and the patient became asymptomatic and was anxious to be discharged from the hospital.

Course after Discharge from Hospital: Three days after leaving the hospital the patient was readmitted to the Nurses' Infirmary because of two shaking chills and nausea. Again the patient reported a temperature of 102.8° F., which was 98° F. 30 minutes later. Physical examination was negative. On the following evening the patient recorded the temperature at 103.6° F., and 30 minutes later, when taken by a physician, it was 98.2° F. Subsequently she remained afebrile.

This nurse posed a considerable problem to the physicians managing her case. The history of biliary tract disease led to serious consideration of a diagnosis of Charcot's intermittent fever. The alertness of the house officer in charge of her case was largely responsible for the fact that the diagnosis of spurious fever was made and confirmed so promptly.

Case 8 (figure 7). A 38 year old man presented with a chief complaint of "blacking-out spells."

He told a complex story that varied widely in the versions given to several observers. Twenty-nine years before admission the patient had been hit by a truck and had suffered multiple injuries, including a skull fracture. Following the accident he gained weight rapidly, and at the age of 26 weighed 420 pounds. (His weight on admission was 325 pounds.) At the age of 24 he was brought to the emergency ward unconscious. The vital signs and physical and neurologic examinations were not remarkable; no diagnosis was made. Similar "spells" had occurred every two to three weeks for several months prior to the present admission. These were ushered in by "weakness and faintness," and lasted about five minutes. The patient stated that he had been pronounced dead during one of these attacks at another hospital. The episodes were not accompanied by abnormal movements or incontinence.

Eight years before admission he had developed severe frontal headaches and transient paralysis of the left arm. These difficulties ceased abruptly after bilateral burr holes were made.

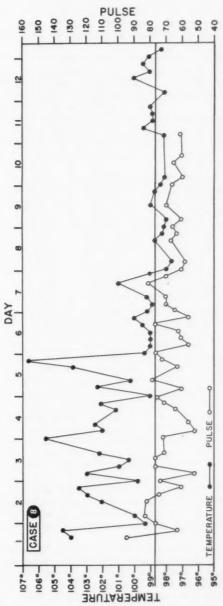


Fig. 7. A 38 year old man with multiple complaints but no significant disease had a heetic fever, which disappeared when the temperature was taken under supervision. He had previously malingered in similar fashion at several other institutions.

In addition, he had had peripheral vascular disease of at least eight years' duration, which had culminated in a midthigh amputation on the left. The extract nature of the vascular difficulty was never elucidated. However, he complained of severe pain in the right leg, and at the time of hospitalization was taking about 400 mg.

of meperidine daily.

Physical Examination: The vital signs were normal. The patient was massively obese and appeared to be in no distress. There were numerous scars. The abdomen was covered with striae albicantes. The left leg had been amputated above the knee. The skull was normal to palpation. The thyroid was not palpable, the testes were atrophic and the penis was small, but the prostate was of normal size and there was a normal amount of pubic and axillary hair. The right leg showed an area of mild chronic stasis dermatitis over the shin; all pulses were easily palpable in the extremity. Neurologic examination revealed a sharply demarcated left hemianesthesia to all modalities, but there was no motor weakness and the deep tendon reflexes and cranial nerves were intact.

Laboratory Data: Extensive laboratory studies were undertaken. The hemogram, urine, stool and serology were normal. The sedimentation rate was 28 mm./hr. corrected. Nonprotein nitrogen, fasting blood sugar, total protein with A/G ratio, calcium, phosphorus, cholesterol and other serum lipids, butanol extractable iodine, and tests of liver function were normal. Cultures of the blood, nose, throat and leg lesion failed to reveal pathogens. Films of the chest, skull, leg and lumbar spine were noncontributory. Excretion of 17-ketosteroids and follicle-stimulating hormone in the urine was within normal limits. The cerebrospinal fluid protein was slightly elevated at 57 mg.%, and the electro-encephalogram showed a "mild diffuse abnormality." The electrocardiogram revealed a sinus bradycardia and occasional premature ventricular contractions; carotid sinus massage failed to alter the record.

Hospital Course: During the first six days in the hospital the patient had several hectic temperature spikes. These were unaccompanied by chills, sweats or change in pulse or respiration. After five days it seemed obvious that the patient was malingering, particularly in the face of a defervescence from 106.6° F. to 99.6° F. in a period of four hours. Thereafter a nurse was always in attendance while the

temperature was being taken, and the febrile spikes ceased.

Extensive psychiatric evaluation, including psychomotor testing, resulted in a diagnosis of "psychopathic personality," with conversion symptoms, reactive depression and mild organic brain disease. The patient left the hospital on the twelfth day.

After discharge several reports from other hospitals were received which confirmed the impression of malingering. There was no evidence at any of these institutions of organic disease, although the admission diagnosis of coronary thrombosis had been made at several. One report stated that the patient had successfully falsified his temperatures by "rectal massage" for several weeks, and that subsequent temperatures taken by mouth were always normal.

Case 9 (figure 8). This 44 year old white man was admitted in 1944 complaining of crushing, oppressive precordial pain which radiated to the left shoulder and down the ulnar aspect of the left arm. The attack had begun suddenly three hours before. He denied any history of prior symptoms referable to the cardiovascular

system.

Physical Examination: Temperature, 99.6° F.; pulse, 102; respirations, 22; blood pressure, 108/58 mm. of Hg. The patient was well nourished and in no apparent discomfort. The skin was warm, and there was no sweating or cyanosis. The remainder of the examination revealed no abnormalities.

Laboratory Data: Serologic test for syphilis negative; hemogram, within normal limits; sedimentation rate on admission, 30 mm./hr. Six days later the sedimentation rate was 6 mm./hr. Urinalysis, nonprotein nitrogen and serum cholesterol were

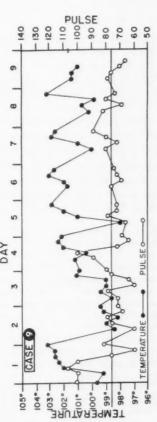


Fig. 8. This 44 year old man entered the hospital with symptoms suggestive of a myocardial infarction. All studies were negative, and it was learned that he had been admitted to many other hospitals with the same complaint. The reason for the "fever" became clear when he was seen holding the thermometer next to a light bulb.

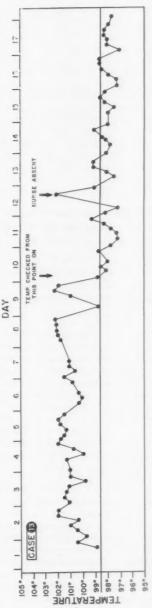


Fig. 9. This patient had been an "F.U.O." for several months until a nurse stayed in the room with her during the recording of temperatures. The sudden recrudescence of fever on one occasion when the nurse was out of the room is particularly noteworthy.

normal. Chest x-ray showed no disease. Serial electrocardiograms were entirely normal and failed to reveal any evidence of myocardial infarction.

Hospital Course: For the first few days in the hospital the patient had persistent pain, for which large doses of morphine sulfate were given. The pain was often so severe that he jumped and tossed about in bed. He became increasingly irrational; he was demanding and hyperirritable, and at times manifested delusional behavior. His course was irregularly febrile, with several spikes to more than 103° F. On several occasions other patients reported that he was seen holding the thermometer next to a hot electric light bulb. Moreover, he refused to have his temperature taken with nurses or doctors in attendance. It is noteworthy that his pulse was usually normal in the presence of an elevated temperature.

Soon after admission it was learned that the patient had been admitted to several hospitals in Baltimore and Philadelphia with an identical story of chest pain, and that at none of these hospitals was any evidence of coronary artery disease found. He was seen by a psychiatric consultant, who made the diagnosis of paranoid reaction in an individual with a rigid personality, and who felt that early discharge was mandatory. This was carried out on the tenth hospital day.

The two cases just described are similar. Both patients were men and were well recognized psychopaths. In both, fever was merely an incidental finding, and was presumably a means of lending authenticity to spurious complaints involving the cardiovascular and central nervous systems. Actually, the obviously abnormal pattern of their fevers was one of the more important clues to the correct diagnosis, and it would probably have been far more difficult to discover the origin of their "diseases" had spurious fevers not been detected.

Case 10. A 34 year old single nurse was hospitalized in July, 1954, complaining of weakness, fatigability and weight loss.

The patient had been in normal health until the summer of 1946, when she had had a succession of upper respiratory infections accompanied by intermittent small hemoptyses, weight loss and pleuritic pain. Chest x-ray revealed a slight pleural effusion, and she was hospitalized for suspected tuberculosis; all signs and symptoms disappeared after four months of bed-rest. No tubercle bacilli were demonstrated by smear and culture of sputum; tuberculin skin test was negative.

In 1947 she had been a patient at several hospitals and sanatoria because of weight loss, chills, fever and hematuria. She was suspected of having tuberculosis of the kidneys, in spite of the fact that acid-fast bacilli could not be demonstrated in bladder and ureteral urine, and cultures, guinea pig inoculation and intravenous and retrograde pyelograms were negative. At this time she had a well documented hypersensitivity reaction to streptomycin and para-aminosalicylic acid. It is of interest that, in retrospect, all reports of positive evidence of tuberculosis were verbal ones by the patient, and that there was never any bacteriologic support for this diagnosis. It is significant that at one hospital she had a persistently elevated temperature despite a normal chest x-ray.

Because of persistent metrorrhagia the question of tuberculous endometritis was raised, but endometrial biopsy failed to confirm this impression. X-rays of the gastrointestinal tract were entirely normal.

The patient recovered spontaneously from all of her symptoms but continued to have vague respiratory complaints, which led to bronchoscopy and bronchography in 1951; all findings were normal. A culture from bronchial secretions failed to grow tubercle bacilli.

The present admission was precipitated by symptoms of fatigability, weakness, insomnia, general malaise and a nonproductive cough which had been present for six months. She had lost 12 pounds during that period. The primary purpose of her hospitalization was to rule out disseminated tuberculosis.

Physical Examination: Temperature, 99.6° F.; pulse, 72; respirations, 16; blood pressure, 120/70 mm. of Hg. The patient was a well developed, well nourished but somewhat asthenic white female in no distress.

The general physical examination, including neurologic evaluation, was entirely within normal limits.

Laboratory Data: Serologic test for syphilis negative; hemogram, normal. Sedimentation rate, 2 mm./hr. (Wintrobe). Urinalysis, entirely normal. Chest film, films of the lumbar spine, and intravenous and retrograde pyelograms were within normal limits. Three 24-hour urines, three 24-hour sputum concentrates, two gastric washings, and washings from the ethmoid sinuses showed no tubercle bacilli on smear and culture, and guinea pigs inoculated with these materials showed no lesions of tuberculosis. Several urine cultures, including ureteral specimens obtained at cystoscopy, were negative.

Hospital Course: The patient was seen in consultation by a gynecologist, who found the pelvic structures to be normal, and who also performed cystoscopy with catheterization of both ureters. There was no evidence of renal tuberculosis or chronic pyelonephritis on this examination. Considerable psychic trauma attended the cystoscopy, and the patient began to manifest infantile and regressive behavior. This was exacerbated by fear and hostility toward a psychiatric consultant. Affect became blunted and psychotic behavior persisted for several days; however, she eventually recognized her need for psychotherapy and permitted transfer to a mental hospital.

Her hospital course was intermittently febrile, with temperatures as high as 101.8° F. There was no apparent cause for the elevation in temperature which, in the light of the patient's other symptoms, was presumed to be factitious, although the mechanism by which the fever was produced was never satisfactorily ascertained.

Follow-up revealed that the patient left the psychiatric clinic against advice two weeks after her admission. One year later she was seen by a surgeon with the complaint of rapidly increasing size of both breasts. On examination the breasts were normal in size and consistency, and it seemed clear that the patient's symptoms were delusional.

This woman, who had a severe personality disorder, utilized a previous illness, probably incorrectly diagnosed as tuberculosis, as a stepping-stone for many symptoms. The reason for the low grade fever was never definitely found, and this may, in fact, represent an instance of "hysterical fever," although it seems likely that the temperature elevations were produced by deliberate trickery.

Case 11. A 51 year old housewife was admitted for evaluation of nervousness, palpitation and progressive weight loss over a period of eight years.

Her illness had begun with the gradual onset of heat intolerance, easy fatigability, weight loss and weakness in the face of a normal appetite. She was seen by a surgeon who was unable to palpate the thyroid and who informed her that the gland could not be removed surgically. The symptoms gradually increased in severity, and palpitation and ankle edema became her prominent complaints. Several measurements of basal metabolic rate had ranged between plus 32 and plus 36.

Physical Examination: Temperature, 99.8° F.; pulse, 100 (apical), 76 (radial); respirations, 24; blood pressure, 125/75 mm. of Hg. The patient was a thin, anxious woman with evidence of chronic weight loss. The skin was warm and moist. The eyes were normal. The thyroid gland was not palpable. Auricular fibrillation was present without other cardiac abnormalities. Except for a fine tremor of the hands, there were no neurologic findings.

Laboratory Data: Hemogram, urinalysis, stool, serum proteins, calcium, phosphorus, alkaline phosphatase and liver function tests were normal. The sedimentation rate was 8 mm./hr. (Wintrobe); cholesterol, 197 mg.%. X-rays of chest and gastrointestinal tract were normal. Basal metabolic rates were plus 40 and plus 26. Radioactive iodine uptake was extremely low, in the range for hypothyroidism; there was no uptake of the I¹³¹ over the lower abdomen. Protein bound iodine was 9 µg.%.

Hospital Course: In the hospital the patient continued to be nervous and overactive. She was intermittently febrile, with temperatures as high as 101.6° F. Blood cultures as well as bacterial agglutinations were negative. No complaints other than mild headache and malaise were associated with the temperature spikes. Auricular fibrillation ceased on the second hospital day and did not recur.

The enigma of the elevated basal metabolic rate in the presence of a slightly elevated PBI, normal cholesterol and very low uptake of I¹³¹ was resolved when a cache of desiccated thyroid tablets was found in the patient's bedside stand. When she was asked to explain the presence of the tablets she promptly signed out of the hospital.

Although fever was not the primary reason for hospitalization of this woman, it was a worrisome aspect of the case and led to extensive laboratory investigation. Whether the temperature elevations were due to ingestion of desiccated thyroid or were induced by mechanical manipulation remains unanswered.

 $\it Case~12.~{
m A}$ 41 year old former Navy nurse entered the hospital for evaluation of her endocrine status.

Her complicated history included a subtotal thyroidectomy for thyrotoxicosis, bouts of tetany both before and after removal of the thyroid, "subacute bacterial endocarditis" and Addison's disease. She had been treated for the latter condition by implantation of DOCA pellets and supplemental dietary salt for several years. There was no documentation for any of these disorders, and the patient refused to elaborate on them in terms of symptoms, preferring instead to confine the discussion to diagnostic terms. For one month prior to admission she had been receiving 5 mg. of DOCA in oil and 6 gm. of added salt per day.

Physical Examination: The vital signs were normal. There was no abnormal pigmentation of skin or mucous membranes. The hair distribution was normal, and no calcification of the aural cartilages was noted. The heart, lungs and abdomen were normal.

Laboratory Data: Hemogram, urine, stool, sedimentation rate, nonprotein nitrogen, phenolsulfonphthalein, serum proteins and electrolytes, tests of liver function and x-rays of the chest and skull were normal. Eosinophil count was 55/mm³.

Hospital Course: The patient's initial blood sugar was 53 mg.%, and several glucose tolerance tests, both chemically and clinically, yielded results diagnostic of hyperinsulinism. This was confirmed by prompt remission of all symptoms upon the administration of intravenous glucose. However, several blood sugars after prolonged fasts were normal, and it was noted in retrospect that the patient had always been forewarned the evening before blood was to be drawn for analysis. Therefore, several "surprise" blood sugars and glucose tolerance tests were performed,

always over the patient's strenuous objections; these were invariably normal. Diseases of the thyroid, adrenal and pituitary were ruled out by appropriate laboratory examinations, and it was concluded that the patient's primary difficulty was a severe psychosis, manifested by self-administration of insulin. When psychiatric treatment was recommended she left the hospital against advice.

Although the hypoglycemic episodes attracted most attention, it is noteworthy that the patient was intermittently febrile during her hospital stay, the highest recorded temperature having been 102° F. It was never clear whether the fever per se was spurious or was secondary to self-medication.

Both of these patients had factitious endocrine disorders, the fever itself being incidental to other manifestations. Whether elevations in temperature were due to the exogenous hormone (particularly thyroid) or were artefactual is not certain. In any case, fever served as a useful adjunct by making the over-all picture of disease more convincing and the detection of deception more difficult.

Case 13 (figure 9). A 37 year old white married woman was admitted to the hospital because of pain and inability to move her legs.

Her general health had been good until six months previously, when she had noted pain in the cervical spine and "low grade" fever. Shortly thereafter she became acutely ill with right-sided pleuritic pain and tender swelling of both knees. She was treated with oral cortisone and the joint swelling subsided, but the leg pain had persisted and had become so severe that she refused to move the extremities and remained in bed with her legs elevated. During the two months before hospitalization she had developed numerous hemorrhagic lesions over the skin of both legs, fresh "crops" appearing about every two weeks. She continued to be febrile and was said to be anemic. Physiotherapy, adrenal steroids and blood transfusions had resulted in no subjective or objective improvement, and she was finally referred to The Johns Hopkins Hospital for management. At the time of admission she was taking 600 to 800 mg. of meperidine daily for the pain in her legs.

Physical Examination: Vital signs were normal. The patient was lying flat in bed with her legs elevated in a wooden frame, complaining loudly of pain. She repeatedly ordered the intern not to touch her legs. Both legs were exquisitely tender, and there was atrophy involving all major muscle groups. The skin of the legs was dry and scaly, and there was a large ecchymotic area over the medial aspect of the right knee. There was stocking hypesthesia below both knees. She was unable to move the legs except for wiggling of the toes on the left foot. The remainder of the examination was normal.

Laboratory Data: Hemogram, urinalysis, sedimentation rate, platelet count, eosinophil count, stool examination, tests of blood coagulation, and many other studies, including renal and hepatic function tests, were normal. No L.E. cells were found. X-rays of the chest, knees and hands were normal. Biopsy specimens of skin, muscle and lymph node showed no lesions. The cerebrospinal fluid was normal, and the concentration of lead in blood and urine was within normal limits.

Hospital Course: During the first nine days in the hospital the patient's oral temperature ranged from 99.6° to 102° F. When nurses were asked to remain with the patient each time temperature was taken the fever subsided, except on one occasion when a temperature of 102° F. was reported after the nurse absented herself from the patient's room for a few minutes (figure 9). On another occasion the patient was seen manipulating a cigarette lighter while the thermometer was in her mouth.

The patient continued to complain of severe pain in the legs, but examination under light Pentothal anesthesia showed normal motor power and response to sensory stimulation. A regimen of physiotherapy and psychotherapy was begun, with considerable improvement. The patient was transferred to a mental hospital for further care and eventually recovered completely.

Although this patient's chief complaint was pain in the legs, thought by a psychiatrist to be on the basis of conversion hysteria, her fever was unquestionably spurious. The isolated spike in temperature on the one occasion when the nurse was out of the room was particularly striking. The patient later admitted that the ecchymotic lesions on her legs were self-inflicted. It is worth emphasizing that this patient responded well to appropriate psychiatric treatment, the only case in the entire series to do so.

DISCUSSION

Elevation of body temperature is not only a reflection of disease states but is also a natural consequence of such physiologic stimuli as strenuous exercise, digestion, heat, ovulation and pregnancy.4 Furthermore, psychic factors have been held responsible for hyperthermia. Osler mentioned fever as a manifestation of hysteria,5 and further subdivided these patients into those in whom fever was the sole symptom, a second group who had spurious symptoms or signs in addition to fever, and, finally, some who had "hysterical hyperpyrexia," and in whom the temperature spiked to exceedingly high levels. He also made the very pertinent observation that hysterical patients have a strong tendency to practice deception. Psychiatric aberrations and spurious hyperthermia are often closely interwoven, and failure to separate genuinely hysterical symptoms from those produced by purposeful trickery has led to considerable confusion, resulting in the use of the terms psychogenic fever, habitual hyperthermia and hysterical fever almost interchangeably. There is ample evidence for the existence of the clinical syndrome of habitual hyperthermia. As defined by Reimann, 6, 7 this disorder is most likely to occur in young women whose body temperatures remain persistently at a level of about 100° F. Many are overtly neurotic. Concomitant complaints include loss of weight, mild anorexia and listlessness. There are many well documented examples of low grade fever brought on by such anxiety-producing situations as clinic visits and venipuncture,8 unrequited love 9 and an inadequate husband.9 In the latter case, divorce was followed by a return of body temperature to the normal range. The mechanism of "fever" in these patients is probably related to lability of thermoregulatory apparatus, which is under the influence of the autonomic nervous system and the hypothalamus. This concept has its counterpart in vasomotor instability, which results in flushing, dermographia, bouts of tachycardia, and even transient hypertension in stressful situations. Indeed, the association of vasomotor lability and "psychogenic fever" is not unusual. It is probable that elevations in temperature of one or two degrees

above "normal" secondary to emotional stimuli are more common than is generally realized. Further studies to clarify this point would be useful.

On the other hand, temperatures above 100.5° F., for which no organic cause can be found, should not be dismissed as examples of "psychogenic" hyperthermia without careful elimination of disease or deceit. Although several cases of long-continued fever classified as hysterical and supposedly not artefactual have been reported in recent years,1,10,11 it is more likely, particularly in the hyperpyrexic group reported by MacNeal,1 that most of these elevations of temperature were produced by fraudulent means. The discovery of the fraud and the way in which it is perpetrated can be attended by considerable difficulty, and in some cases much time, effort and ingenuity are required before the riddle is solved. In four cases reported by Schnur 12 it required from three to eight months to marshal conclusive evidence for malingering. Proof of factitious origin of fever in several other reported cases 1, 2, 11, 18 was equally time-consuming and tedious. In the present series the evidence for trickery was incontrovertible in only 10 of 14 cases. One may reasonably suppose, however, that hyperthermia in the remainder was spurious.

There are several clues that call attention to the possibility of spurious fever: (a) failure of the temperature curve to follow the normal diurnal gradient of body temperature—higher in the late afternoon and early evening; (b) absence of tachycardia in the face of abrupt spikes in temperature; (c) strikingly rapid defervescence unaccompanied by diaphoresis; (d) presence of fever of 106° F. or higher, a relatively rare phenomenon in adults. It should be pointed out that nurses, doctors and others familiar with hospital routine are particularly prone to this form of malingering. Five patients in this series, as well as those reported by Schnur 2 and Hale, fell into this category. Once the diagnosis has been considered, it is best confirmed by having an attendant hold the thermometer in place. Because of the curious ability of some patients to manipulate their rectal sphincters, readings should be taken in at least two separate locations. If the issue is still in doubt, testing freshly voided urine will sometimes aid in determining the true temperature of the internal environment.

The technics by which temperatures have been falsified are numerous and varied, and attest to the ingenuity of patients who practice this form of deception. Among the more commonly used methods are holding the thermometer next to a hot water bottle, steampipe, light bulb or flame, rubbing the instrument against the bedclothes, shaking it in retrograde fashion, and manipulating the teeth, gums or anal sphincter to produce friction. A more sophisticated maneuver is to keep a cache of thermometers set at various readings, and to substitute one of these for the one distributed by the nurse. This trick was used with great success by one of the patients in this group (case 3). There have been a number of cases 13, 15, 16 in which patients have injected themselves with vaccines, toxoids and pyrogenic

materials, thus producing bona fide hyperthermia by fraudulent means. Self-catheterization may have contributed to the fever of one patient in the present series (case 6), although other mechanisms were probably operative as well.

The association of spurious fever with other factitious disease is frequent, and it may be difficult to decide whether the fever itself has been fraudulently induced or whether the elevation in temperature is genuine but secondary to some other artefactual lesion. It is well, however, to remember that fever occurring in the presence of factitious disease is likely to be the result of deliberate trickery.

The management of these patients, once the hoax has been discovered, presents a serious problem. Often they wander from hospital to hospital (cases 4, 8, 9 and 10), and characteristically leave against advice when the true state of affairs becomes known and the subject of psychiatric treatment is mentioned. An even more difficult problem in disposition is the patient who is found to be malingering for the first time and who has no previous history of psychiatric disease (cases 1, 1a, 2, 7, 11 and 13). As can be seen from the present series, in most cases the motives for deception and the underlying psychic disturbances were not elucidated and the patients were discharged as quickly as possible.

The purpose of this report has been to call attention to a situation which is often neglected in considering the etiology of obscure fever. It is not meant to imply, however, that many or most fevers are factitious, or to discount the importance of diligent searching for other causes of pyrexia of unknown etiology. Similarly, it should be pointed out that fever in the hysterical patient more often than not is genuine rather than spurious. On the other hand, if spurious fever is kept in mind, a great deal of needless "laboratorizing" can be eliminated by the simple expedient of having a physician or nurse at the bedside while the temperature is being taken. Before facing the diagnostic enigma so often presented by a case of "F.U.O.," one should be sure that the "F" component is present.

SUMMARY

Fourteen patients with pyrexia produced by fraud are reported. Twelve of these were women, and five were nurses. Many had a history of similar episodes in the past, and several had other factitious diseases, such as hypoglycemia secondary to exogenous insulin, thyrotoxicosis due to consumption of large doses of the hormone, hematuria, purpura or dermatitis. Methods of production and signs leading to recognition of this syndrome are described. The relation of factitious fever to psychogenic fever and habitual hyperthermia is discussed.

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SUMMARIO IN INTERLINGUA

Ben que febre occurre como manifestation de multe morbos de diverse etiologias, il es le responsabilitate del medico-ante que ille initia le longe, tedie, e frequentemente costose cerca del causa del febre-determinar que un elevation del temperatura corporee existe vermente. Le presente reporto concerne 14 casos de "febre de etiologia non cognoscite" in que il habeva bon rationes pro creder que anormalmente alte temperaturas esseva registrate per medios deliberatemente fraudulente. Dece-duo del patientes esseva feminas con un etate medie de 32 annos. Cinque de illas esseva infirmeras. In octo casos, febre esseva le gravamine principal. In le remanente casos, altere disturbationes-usualmente non minus apocryphe-esseva le causa del hospitalisation, e le constatation del elevate temperatura esseva un constatation incidental. In dece-duo patientes le false temperaturas variava ab 101 F usque a 105,6 F. Duo habeva febres de plus que 106 F. Le episodios de febrilitate durava inter 10 dies e sex menses, e plures del patientes habeva repetite attaccos de pyrexia. Le mechanismos usate in le production del false temperaturas variava extensemente. Un certe numero del patientes succuteva le thermometro in position inverse; alteres frottava lo contra le pannos de lecto o approchava lo a lampas o incensores mechanic. Un del patientes habeva un celate stock de thermometros adjustate a varie temperaturas, e duo manipulava lor sphincteres anal de maniera a producer un elevation del temperatura. Un del damas esseva le victima de su infirmera private qui reportava febre pro prolongar su empleo. Finalmente le diagnose esseva establite per le decision que le medico mesme insererea e sustenerea le thermometro, e iste mesura es recommendate in omne patientes con suspicion de febre facticie.

Le conditiones associate incontrate in un certe numero de iste patientes includeva thyrotoxicosis autogenerate, hypoglycemia facticie, e autogenerate purpura, hematuria, e dermatitis. Duo alteres se plangeva de dolores abdominal e un de episodios de perdita de conscientia.

Le majoritate del patientes habeva sever subjacente disordines psychiatric. Le regime esseva uniformemente non-satisfactori, in certe casos proque le uso de mesuras psychotherapeutic esseva rejicite e in alteres proque le patientes esseva considerate como pauco promittente candidatos pro ille typo de therapia.

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THE PSYCHOSOMATIC APPROACH IN MEDICINE *

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From a multicausal point of view, psychologic factors play a rôle in all disease processes, although the importance of this rôle is highly variable. Lewis 2 estimated, as a result of his evaluation of recent psychomedical surveys, ". . . that psychological disturbances were responsible, wholly or in part, for the illnesses of . . . 47% of . . . medical patients " The patients he studied were representative of the type usually seen in general practice. The disorders Lewis considered to be psychogenic included those which are wholly psychologic or functional in origin without any demonstrable organic etiology or tissue damage, e.g., conversion hysteria and hypochondriasis, as well as certain disorders manifesting demonstrable pathologic changes that are assumed to have significant psychic causes and are usually designated as psychosomatic diseases, such as peptic ulcer and ulcerative colitis.

The authors believe that the general physician or internist can often successfully treat both the physical and the emotional aspects of such psychosomatic illnesses. Since the internist sees the psychosomatic patient early in the course of the disease, when the causative psychogenic factors are most recent, superficial and amenable to therapy, he is in a position to treat them when they are most accessible. In addition, some patients in the early stages of their illness may resent referral to a psychiatrist but will accept psychotherapy from their medical physician. The psychotherapeutic approach to be presented in this paper can be used by the general practitioner or internist and is particularly applicable in the management of psychosomatic disorders. On the other hand, diseases such as hysteria and hypochondriasis are psychiatric illnesses specifically requiring treatment by a psychiatrist.

Psychophysiologic autonomic and visceral disorders 3 or, by more common usage, psychosomatic diseases, are physical illnesses which are precipitated or sustained by emotional factors. According to current theory, psychosomatic disease is largely the autonomically mediated, physiologic accompaniment or result of chronic intense emotional states. For example, the increased gastric motility and hydrochloric acid secretion resulting from chronic anxiety 4 play a significant rôle in the causation of the structural

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pathologic changes seen in peptic ulcer. The psychologic stress contributing to the development of psychosomatic illness is probably nonspecific and may derive from any source. Emotional factors may have varying degrees of etiologic significance in different psychosomatic diseases and in different patients. The most frequent causes of the chronic intense emotional states, which contribute to the genesis of psychosomatic disease, are neurotic conflicts, disturbed interpersonal relationships, and self-defeating patterns of behavior. Only by resolving the underlying neurotic patterns and conflicts through psychotherapy can the undesirable chronic emotional state be alleviated.

Since it is the goal of medical practice to diminish or remove all causative agents contributing to the development of a disease, and since psychogenic factors may be of the utmost etiologic importance in many diseases, such emotional factors must be taken into consideration in the total treatment of the patient. Since psychologic diagnosis and treatment present a unique problem in medical practice, in that the technics of psychiatry are radically different from the usual medical technics, this paper on psychosomatic management has been written in the hope that it will be helpful to the physician in expanding his total therapeutic approach.

Among the diseases in which psychic factors appear to play an important role and which are classified as *psychosomatic disorders* are: Angina pectoris; severe allergic reactions; anorexia nervosa; biliary dyskinesia; bronchial asthma; cardiospasm; cardiovascular neurosis; colitis (atonic, mucous, spastic and ulcerative); coronary heart disease; diabetes mellitus; essential hypertension; globus hystericus; hay fever; hyperthyroidism; migraine and other headaches; neurocirculatory asthenia; nervous stomach; obesity; peptic ulcer; pruritus ani; pylorospasm; Raynaud's disease; rheumatoid arthritis; regional ileitis; skin diseases (such as eczema, neurodermatitis, warts, angioneurotic edema); tuberculosis; urticaria; vasodepressor syncope (fainting), etc.

In addition to the aforementioned group of *psychosomatic diseases*, there is a much larger number of *psychosomatic symptoms* which, though usually resulting from organic dysfunction, may frequently be predominantly psychogenic in origin. Among them are:

Bone and Joints: Arthralgia; back pains; growing pains

Cardiovascular: Chest pain; dyspnea; heart pounding; orthopnea; palpitation; bradycardia; tachycardia

Gastrointestinal: Abdominal pain; abdominal cramps; anorexia; belching; bulimia; dysphagia; constipation; diarrhea; dyspepsia; flatulence; flatus; nervous stomach; nausea; tenesmus (anal spasm); vomiting; heart burn; borborygmi

Genitourinary (Female): Amenorrhea; dyspareunia; dysmenorrhea; frigidity; leukorrhea; menopausal syndrome; nymphomania; premenstrual tension

Genitourinary (Male): Impotence; male climacterium; premature ejaculation; satyriasis; urinary frequency; urinary urgency; urinary burning; itching

Muscular: Paralysis; spasm; tremor; pain; weakness; aching; breast

pain; loss of weight; trembling

Neuropsychiatric: Neuralgia; insomnia; fatigability; faintness; dizziness; anesthesia; paresthesia; numbness; tiredness; seizures; weakness; tinnitus; headache; irritability; restlessness; jitteriness; tension; anxiety; "lightheadedness"; nervousness

Respiratory: Coughing; hyperventilation; choking; singultus; sneezing; difficulty in catching one's breath; breathlessness

THE PSYCHOSOMATIC EVALUATION

In the medical evaluation and therapeutic management of any disease which has significant contributory psychogenic factors, it is essential that the psychic as well as the physical disturbance be taken into consideration. When the general medical practitioner is confronted with a disease or symptom in which psychogenic determinants seem to be important, he must evaluate it from a total, *comprehensive* or *psychosomatic* viewpoint. It is the aim of a psychosomatic evaluation to elucidate the nature of and the interrelationship between the physical and psychologic factors that contribute to the development of the disease in question.

The first step in the comprehensive evaluation of the psychosomatic patient should be a complete medical study, including a careful medical history, physical examination and laboratory work-up. The immediate reason for the patient's seeking medical consultation should be determined, particularly where his illness or symptom is chronic in nature. The patient's complaints and symptoms must be exactly defined by intensive questioning. For example, if the patient's chief complaint is "pain," the location, degree, duration and temporal pattern should be determined. Factors modifying the symptom, such as the circumstances under which it is intensified or diminished, as well as any previous medical treatment of the complaint, should be noted in order to define more clearly the diagnosis, management and prognosis of the illness causing the symptom. Are the symptoms appropriate to an organic picture, or are they characterized by the bizarreness, irregularity and lack of predictability that usually indicate a functional disorder? The patient should be questioned about past and present psychosomatic and psychiatric disturbances. During the routine medical history, the psychologic factors surrounding the patient's disorder require close scrutiny. Psychologic exploration should be carried out in a relaxed, informal and nonthreatening manner. It should be smoothly integrated into the total medical examination. In the course of the usual eliciting of the history of the illness, the physician should question the patient in detail about the life situation and psychologic factors that surround the onset, exacerbation and remission of

his symptoms. It is particularly valuable to attempt to obtain from the patient an accurate account of the sequence of events related to the development of his psychosomatic illness. While occasionally a cause-effect relationship between emotional stress and physical disease can be elicited on superficial questioning, the patient is usually not aware of any such relationship, and it can be established only by careful interrogation. At other times, an inverse cyclic relationship between psychic illness and physical symptomatology is quite apparent—that is, when the patient is physically well his psychologic symptoms become aggravated, and when he is psychologically asymptomatic his physical difficulties become worse. In order to discover the relationship between psychic and somatic factors, it may prove helpful to determine such things as the past and present attitude of the patient and his family toward his psychosomatic illness, and how the disorder affects his daily interpersonal relations and life situation. For example, if the patient shows excessive concern or if he is unduly apathetic to his condition, either reaction may be suggestive of a significant psychologic component in the patient's illness. What is the degree of disability resulting from the illness? What gratifications are derived from, and what activities are prevented by, the patient's disease? It should be noted whether there are any secondary gains accruing from the illness, e.g., the satisfaction of certain childish dependency needs that patients often receive when they are sick may unconsciously reinforce their remaining ill. Psychosomatic disease may help a patient to avoid certain painful situations; for example, such a disorder may be a passive patient's only means of expressing aggression against his mother or boss. The patient's motivation for getting help must be evaluated; does the patient seem able and desirous of understanding and resolving his psychosomatic difficulties?

After the doctor has diagnosed the physical aspects of the patient's somatic illness and has concluded as a result of his psychosomatic evaluation that psychologic factors are etiologically significant, he is ready to formulate his plan of treatment. While the physician will continue to treat the somatic aspects of the case, he may take one of the following courses in his management of the patient's emotional difficulties: (1) When the patient has a serious psychiatric disturbance * in addition to his somatic disorder, he

^{*}The authors would include under the heading of serious major psychologic disturbances that usually require psychiatric intervention by a psychiatrist: (1) a severe anxiety neurosis; (2) suicidal or homicidal preoccupation or threats; (3) a moderate to severe neurosis, or neurotic symptoms, such as a phobia, obsessive-compulsive neurosis, conversion hysterical or dissociative reaction, neurotic depression and hypochondriasis; (4) a moderate to severe character neurosis, such as a passive-aggressive, inadequate, emotionally unstable, paranoid, schizoid, cyclothymic, compulsive and sociopathic (dyssocial, antisocial, sex deviation, drug addiction) personality disturbance; (5) all psychotic syndromes—paranoid state, paranoia, involutional depression, psychotic depression, manic-depressive psychosis, schizophrenia, senile psychosis, and the symptoms of these psychotic syndromes such as loss of contact with reality, delusions, hallucinations, illusions, ideas of reference, feelings of depersonalization, etc. In a broad sense, patients with these serious psychologic problems have marked difficulty in getting along with people and have a great deal of anxiety arising from this interaction. There is an occasional exception to the aforementioned indications for psychiatric treatment by a

should be referred to a psychiatrist for evaluation of his psychiatric status. (2) When the patient's psychologic problems are of a superficial nature,† and the somatic illness is of sufficiently recent origin, the physician may decide to treat the psychogenic as well as the somatic factors himself. This situation is the most usual one. (3) In patients who are suffering from chronic, long-standing psychosomatic diseases, characterized by periodic remissions and exacerbations, psychiatric referral is indicated whether or not the psychogenic factors are apparent or even considered significant by the general physician. Such chronic disease processes almost always have serious psychic components, but the psychogenic factors may be hidden behind somatic symptoms. Such patients should invariably be referred for psychiatric consultation.

PSYCHOTHERAPEUTIC MANAGEMENT

Anxiety and other chronic intense emotional states contribute to the genesis and progression of psychosomatic illness. These harmful emotional affective states result from the neurotic patient's conflicts and disturbed behavioral patterns. In the superficial psychotherapeutic management of the psychological aspects of the psychosomatic patient's illness as practiced by the internist the goal is to diminish permanently ‡ the patient's anxiety by helping him more clearly to define and resolve certain of his superficial emotional problems. In this technic, the patient is encouraged to talk about himself using the structure of his life experience as the means of communication. By encouraging the patient to relate in an open, honest manner, the physician is laying the groundwork for the development of a trusting warm doctor-patient relationship. By means of such a relationship, the doctor can influence the patient to change constructively. This relationship represents the beginning and basis of psychotherapy. It is this therapeutic relationship which is the key factor in the success of psychological treatment.

psychiatrist; as, for example, in the case of a chronic schizophrenic who is nonamenable to intensive psychotherapy but who requires long-term supportive treatment. Under certain circumstances this supportive therapy may be carried out by the general practitioner.

circumstances this supportive therapy may be carried out by the general practitioner.

† The authors consider emotional difficulties that are of recent acute origin, and that usually involve difficulties in conscious interpersonal, social, work, environmental and marital relationships, as often representing problems of a superficial nature, particularly when the personality adjustment of the individual has been good up to the time of onset of the emotional difficulties. This category includes the group of reactions called transient situational personality disorders. These are "reactions which are more or less transient in character and which appear to be an acute symptomatic response to a situation without apparent underlying personality disturbance. In the presence of good adaptive capacity, recession of symptoms generally occurs when the situational stress diminishes." S Also, patients with mild anxiety and depressive symptoms, mild personality disorders, as well as mild or poorly defined neurotic symptoms and syndromes, may often be given a trial at superficial psychotherapy by the general practitioner. Although patients who have mild dependency and affection problems, superficial problems over hostility, envy, jealousy, assertiveness and withdrawal may be handled with superficial psychotherapy, when these problems are moderate to severe the patient should be sent to a psychiatrist for consultation.

‡Tranquillizing drugs such as Miltown and Atarax offer only a temporary palliative relief of anxiety; they are of minimal value in affording a long term decrease in anxiety and therefore are most limited adjuncts in the management of psychosomatic disorders.

Psychotherapy is initiated by the doctor having a series of "talks" with the patient. This may be accomplished by the doctor setting aside sufficient time for the patient to discuss himself with the physician. For example, it would seem advisable for the physician to allocate a regular period of an hour or two per week for several weeks in which to see the patient. Sessions should be private with no one else present or able to hear what transpires in the doctor's office. During this period the patient is encouraged to discuss his problems with the doctor in a relaxed and leisurely atmosphere, so that he is made to feel that he has sufficient time at his disposal. The physician may initiate the discussion by asking, "Tell me about yourself as a person," or "Tell me about your life or any problems that are bothering you." He should encourage the patient to be spontaneous, frank and honest. The doctor may point out to the patient that he believes his present life situation and emotional problems are aggravating his somatic illness, and that it is necessary to study the patient's background in order to understand his total psychosomatic problem. Initially, the patient should be encouraged to talk freely and to take any direction he wishes in discussing himself with the doctor. Most patients will usually start with their present, more immediate difficulties, because these are of paramount current interest, and will eventually work into their past history. Usually the patient is afforded a wide latitude in his discussion. The physician's attitude should be warm, flexible, sympathetic, tolerant, reassuring; he should be encouraging, nondirective and nonjudgmental. It is important that good rapport develop between patient and doctor. Patience, willingness to expend the necessary time and effort, a basic intellectual honesty, the conviction that psychic factors can play a role in the genesis and progression of organic disease, and belief in the ability of people to change are requisite attitudes for the physician utilizing this psychotherapeutic approach. The patient should be assured from the start that everything he tells the doctor is completely confidential. The physician should never attempt contact with any of the patient's relatives (which may occasionally be necessary and helpful) without the patient's knowledge and permission. The doctor takes the role of the patient's confidante, friend and protector; he is interested in him as a person. It is important for the physician initially to use care in questioning the patient about delicate or traumatic emotional problems, and to refrain from asking questions prematurely which might be distressing to him. While at times the physician may be critical of the patient's behavior, criticism should not be given until a firm, positive relationship exists between doctor and patient, and it should be constructively and never hostilely motivated. Argument, coercion and punishment have no place in the psychotherapeutic relationship. It is wise for the physician practicing superficial psychotherapy to recognize not only what he can do but also what he cannot do. He must determine his limitations in the area of psychotherapy, not only those deriving from his limited training in psychotherapeutic technic, but also those arising from his

own personal problems and prejudices. If the physician does not feel emotionally equipped to attempt psychotherapy, or does not have the time or inclination to do so, it is wise for him to send his patient to a psychiatrist for a psychiatric consultation after he has completed his psychosomatic evaluation. On the other hand, while psychoanalysis and intensive psychotherapy are skills that should be used only by the trained psychotherapist, in many cases a great deal of symptomatic relief and help may be given to the psychosomatic patient through the application of the technics of superficial psychotherapy by the general practitioner.

As noted before, the technic of psychotherapy consists of the discussion of the patient's life history and experiences with him in order to give him some increased understanding of his emotional conflicts, and to help him to resolve some of those conflicts by changing his behavior. This behavioral change, in turn, will diminish the patient's anxiety and thereby help his somatic illness. In this technic, exploration of the patient's present-day activities, as well as his background and past history, and demonstration of the means by which his past influences the present are important. Some of the developmental periods and some of the life experiences offering fruitful areas for investigation are listed below. This should not be taken as a rigid outline of material that has to be elicited specifically from all patients; many patients will not remember or will not be informed about much of these data. It is given only as a rough outline of some significant areas that may be psychodynamically important in many patients.

A. The Patient's Current Functioning and Problems. It is important to evaluate current problems in order to determine the manner in which the patient's symptoms fit into his present life situation. We do this by studying his relationships and interaction with the people in his social milieu.

1. Behavior in Interpersonal Relationships:

(a) The Patient's Interaction with People: What are the patient's outstanding personality characteristics? What are the patient's chief emotional problems, symptoms and conflicts, and how do they affect his functioning with people? How does the patient's present evaluation of himself and his difficulties compare with his self concept and evaluation of his problems in the past? What is the patient's understanding of his psychosomatic disease? How does the patient relate with people; does he have any close friends; is he at ease with people, or is he aggressive, retiring, sensitive, moody, irritable, shy, etc.? Does he want to be close to people? Does he have excessive anxiety, insomnia, or extremes in appetite or bowel function? Does he smoke, drink or take drugs? What are his chief habits? What are his religious attitudes, and how do they affect his functioning and relating to people? Has he any intense hatreds, biases or prejudices? Does the patient

feel frustrated in the gratification of his creative potential or needs? Is the patient overly sensitive about his age, sex, race or nationality?

(b) The Patient's Interaction with the Physician: The doctor can learn much about the patient's problems and behavior by observing carefully, and being sensitive to, the interaction between himself and the patient. Not only will changes in the patient's overt behavior often indicate the nature of certain of his unconscious problems, but the doctor will see at first hand, in the structure of his relationship with the patient, the difficulties the patient has with others.

The physician should be aware of the patient's appearance and behavior during the psychotherapeutic interviews. The patient's attitude toward the doctor and psychotherapy, his facial expression and the inflections and quality of his voice, and whether the patient relates in a dependent, submissive, polite, relaxed or hostile manner, are important clues to the patient's difficulties and should be noted. If the patient's speech is coherent or incoherent, if he is oversensitive, or if he blocks, is evasive or is untruthful, this may indicate significant sensitive personality areas or even serious psychologic abnormality. The patient's emotional state and mood (anger, anxiety, depression, etc.) and the stimuli that elicit these reactions are important. The physician should note whether the patient relates in a warm way, and is capable of forming a close relationship with him, or whether he is guarded, frightened or withdrawn. In addition, it is wise for the physician to try to be aware of his own emotional reactions to the patient, e.g., such negative feelings as mistrust, fear, hostility or dislike of the patient, as well as the opposite of these impulses, are important and should be noted. If the doctor feels negatively toward the patient he should not handle him psychotherapeutically, and even in his medical contact with him should make an effort to control and understand these impulses.

2. The Patient's Present Day Home Environment and His Relationships with People in It: This concerns the nature of the patient's current home environment, its influence upon the patient and how it can be changed.

What is the patient's environment and home situation? Where does he live, whom does he live with, and what is the nature of his relationship with these people?

(a) If he is married, how does the patient get along with his wife and children? What is the patient's marital sexual adjustment? Is the marriage basically sound? Is the relationship a constructive one, or are there destructive elements in it? Do the aims, needs and valuations of husband and wife harmonize? What needs are being met and which ones frustrated? Are there children? How is their adjustment and how do they get along with the patient? If there are no children, why not? Is there any history of extramarital sexual relations? How did he meet his wife and how did their engagement progress? How does the patient feel about his in-laws, and how does his mate feel about his parents?

(b) If he is single, what is his sexual situation? Does he date the op-

posite sex? Why is he single?

3. The Patient's Interpersonal Relationships with His Family and His Familial Genetic Background: Both the influence of heredity and the effect of the childhood environment on the development of the individual are important in understanding the patient's current emotional problems in that his present difficulties have evolved from his past.

What is the socio-economic and cultural background of the individual? What are the ages and health of his parents and siblings? Were there any familial psychosomatic illnesses? What was his parents' marital adjustment? Who was the dominant figure in his parents' home? How does the patient get along with his parents and siblings? What is the nature of their past and present emotional adjustment? What are their educational backgrounds and occupations, and how successful in life are they? What are their present and past personality traits? Is there a familial history of mental disorder or psychosomatic illness? Is there a history of epilepsy, alcoholism, etc.?

- 4. The Patient's Job Situation, Past and Present, and His Interpersonal Relationships at Work: What type of work does he do? What is his relationship to his employer and fellow workers? Does he like his work? How did he get into this particular occupation? What is his education, training, past work experience, ambition, and degree of success? What is his economic situation? Are there any stresses on the job? How does his present position correlate with his self-concept and values?
- 5. Psychosexual: The authors feel sexual function is important because of the significant role it plays in the life of the individual. Malfunctioning in this area results in a great deal of anxiety. In addition, the sexual area is one of the first physiologic functions adversely affected by emotional conflict, so that it warrants examination as one of the major areas of emotional difficulty. However, it is a sensitive area and most patients discuss sex with reluctance.

How does the patient function sexually? What is his past history of sexual experience? What was his parents' attitude toward sex? How did the patient first acquire sexual knowledge? What has been the patient's experience in the area of early crushes, sexual curiosity, petting parties, menses, wet dreams, pubertal masturbation, adult masturbation, sexual perversions, and contraception? Has the patient ever had difficulty in his sexual functioning, such as impotence or frigidity? Is there guilt about sex?

B. The Patient's Developmental History. Very often, exploration of this area will yield a good idea of the severity of the patient's emotional difficulties. For example, if the patient showed maladjustment early in life, his present difficulties are probably profound and deep-seated. On the other hand, if his life has been characterized by a good adjustment up to the time

of the onset of his present illness, the prognosis is more favorable, and prob-

lems are more readily treatable on a superficial basis.

1. Infancy and Childhood: What memories does the patient have about his childhood? Was his childhood a happy or an unhappy period? Was he a wanted child? Who played the dominant role in raising him? Was he breast or bottle fed, and was there any difficulty in weaning? Was he considered precocious or slow intellectually? Did he walk, talk and teethe at a normal age? What was the nature of his infantile feeding behavior, childhood eating habits, and bowel training? Was discipline strict or easy? Was he frail or strong? Were there any indications of childhood emotional disturbance, such as excessive thumbsucking, nail-biting, temper tantrums, infantile masturbation, speech difficulties, tics, night terrors, phobias, nightmares, stealing or lying? Was there enuresis or soiling to an unusual age? As a child, what was the patient's personality—was he shy, restless, placid, overactive, spoiled, overly aggressive or repressed? How did the patient's family react to him when he was a child? Was there any rivalry with siblings?

2. Period of Schooling and Adolescence: How did he get along in school? What was his attitude toward his schoolmates? Was he a leader or a follower? How were his grades, and what were his interests and favorite subjects? Did he participate in extracurricular activities and sports? What was his social adjustment to the same and to the opposite sex? Was he graduated from high school? college? Was the patient in military service and, if so, what was his adjustment, and what were his experiences?

3. Past Illnesses: Many adult psychosomatic patients have past histories of psychosomatic and psychiatric disorders existing before the onset of their present psychosomatic disorders, and these may play a role in helping to precipitate their present somatic illnesses. Also, somatic disease of certain organ systems in childhood may predispose to the development of adult psy-

chosomatic disorders involving these organs.

Determine whether the patient has had any psychosomatic symptoms or disorders in the past. Was there any predisposing organic disease of the involved organ systems during childhood? Was treatment received for these illnesses, if any occurred? What was the parental attitude toward the patient's illnesses when he was a child? How did the patient react to his childhood illnesses? Determine the time, type and duration of any previous emotional disorders, the extent to which the patient has been incapacitated by them, and whether hospital or office treatment was necessary.

The physician may utilize a variety of superficial psychotherapeutic ap-

proaches during his discussions with the patient:

1. Emotional Support: The patient receives a great deal of emotional support merely from his warm and encouraging relationship with his doctor; in addition, he may derive much gratification from his dependency on this "omnipotent" adviser. The feeling of acceptance inherent in the psycho-

therapeutic relationship is important to the patient who feels unwanted and unloved. At times the physician may offer the patient reassurance about his emotional problems and his physical illness. Much support, in fact, may be derived from the patient's realization that he and his symptoms are important enough to be listened to, and from the knowledge that somebody is sufficiently interested in his problems to help him. Furthermore, the patient gains strength from the psychotherapeutic relationship in that he automatically tends to identify with, act like and assume some of the values of the doctor, and to adopt some of his more adequate personality characteristics.

2. Emotional Ventilation and Catharsis: During his interviews with the doctor the patient is encouraged to express himself freely by verbalizing his feelings of anxiety, hostility and guilt. He is able to discuss openly forbidden impulses and conflicts with his nonjudgmental and accepting doctor. He is given the opportunity to unburden himself and thereby to achieve a certain decrease in tension. He may verbalize feelings he might have previously felt were unacceptable, guilt-provoking or even "insane"; through this "psychocatharsis" he will find understanding and tolerance. It is essential that the physician be prepared to expect and to accept in an understanding and impersonal manner the expression of such "dangerous" impulses as hostility, love and dependency, which may at times be directed even toward the doctor. By repeatedly discussing his problems and conflicts the patient will become less sensitive—or desensitized—to them. These aforementioned ventilative activities serve to lessen the patient's anxiety which, in turn,

diminishes his somatic symptoms.

3. Redirection and Reëducation: As a result of the warm, close relationship that develops between doctor and patient, the latter learns to trust his physician. The doctor may give the patient concrete advice, suggestions and direction in solving certain of his problems. He may correct certain of the patient's misconceptions and misinterpretations of reality and of people. At times, the physician may teach the patient healthier modes of behavior; for example, he may encourage the lonely bachelor to have more social contacts with women, and to seek close human relationships, and may make concrete suggestions as to how to accomplish these things. The physician may give the patient new information; for example, it is often very helpful to explain to patients the meaning and the physiologic mechanisms behind their psychosomatic symptoms. Their physical illness and its exact extent should be explained to them. Patients often have bizarre and frightening fantasies about their diseases and imagine them worse than they really are. Some secretly fear that their symptoms are being produced by cancer. doctor can readily clarify these situations when he is aware of their existence and meaning. The doctor may advise the patient to read some material that might broadly discuss the emotional origin of physical symptoms; a book such as The Story of My Psychoanalysis, by John Knight, which tells of a chemist suffering from a bleeding peptic ulcer whose psychosomatic

condition benefited from psychotherapy, is helpful for this purpose. The doctor may explain to the patient the effect of his childhood as well as of his current life situation upon his physical symptoms. In a sense, the patient receives a *reëducation* in treatment.

4. Environmental Manipulation: In the course of therapy the physician may conclude that various persons or situations in the patient's environment are detrimental to his emotional and physical health. He may decide to remove the patient from a difficult situation by hospitalizing him at the time of a physical or psychologic crisis. He may recommend a modification or change in the environment. At other times he may get in touch with members of the patient's family and discuss the patient's situation with them in order to enlist their further coöperation; the doctor thus may, even indirectly, have to treat the patient's relatives. This familial manipulation may serve to improve the relationship between the doctor and the patient, who will see in the doctor someone who not only verbalizes interest in him, but is also willing and able to demonstrate this interest by interceding in his behalf.

5. Interpretation (or Giving of Insight): Superficial psychotherapy of the type being discussed in this paper does not emphasize giving the patient a great deal of understanding about the basic causes of his difficulties; it is essentially superficial in that symptomatic relief is sought through the application of uncomplicated psychologic technics rather than cure of the patient's emotional difficulties. Psychoanalysis or intensive psychotherapy is required for cure of significant emotional problems. However, these are interpretative technics which are tools to be used only by the fully trained

psychiatrist.

In superficial psychotherapy, it is desirable to help the patient to achieve some understanding and resolution of his problems and conflicts in order to produce a limited degree of behavioral change and a diminution in anxiety which should favorably affect the patient's somatic symptoms. However, it is wise for the general practitioner who attempts such limited interpretation of the patient's conflicts to be certain that this is carried out with the greatest of caution, and only when understanding is close to the patient's awareness and near to consciousness. Interpretation of a patient's underlying motives and problems, such as homosexual impulses of which the patient may not be aware, or hostility toward loved ones, may be frightening and shocking and may have undesirable and even dangerous results. Thus, even though the practitioner may have become aware of certain of the patient's deep-seated problems, he should refrain from pointing these out to the patient unless the latter raises them himself. It is particularly helpful in psychosomatic disease that, when a definite relationship can be demonstrated to exist between psychic stress and exacerbation of physical symptomatology, it be interpreted and explained to the patient and an attempt made to correct the difficult situation. Very often when interpretations are too sudden, premature, or given when conflictual material is not sufficiently

near consciousness, excessive anxiety may result which, in turn, may produce an exacerbation of the patient's somatic illness or cause new psychologic symptoms to develop. Thus the general practitioner should be cautious whenever he attempts even limited psychologic interpretation. Those readers interested in a more comprehensive discussion of the principles of superficial psychotherapy may refer to the excellent texts by Levine ⁶ and Wolberg ⁷ on the subject.

During the psychotherapeutic interviews the physician should also prescribe and administer necessary medical treatments. For example, in peptic ulcer the prescription of dietary control, antacids and anticholinergic drugs may be indicated. It is helpful for the doctor to explain the rationale behind

the use of various drugs.

After handling various psychosomatic patients in the aforementioned manner, the physician will soon learn the type of patient and illnesses he works best with.

However, if the patient does not respond to the comprehensive therapeutic management of the general practitioner within a period of several weeks and the psychosomatic disorder continues unabated, it is advisable that he be referred to a psychiatrist for a psychiatric evaluation. It is essential that when the physician has decided to refer the patient for a psychiatric consultation, the latter be properly prepared for his visit to the psychiatrist. When the referral is suggested it is important that the patient not feel rejected by his practitioner. Many patients and doctors have fears and prejudices about psychiatry; some people believe, for example, that going to a psychiatrist is "bad," and tantamount to being insane. The physician can readily dispel these fears by expressing his confidence and belief in psychiatry, and by explaining to the patient that a consultation with a psychiatrist is much the same as consultation with any other medical specialist. The practitioner must be careful not to deprecate psychiatry in any way, and he must avoid making any critical remarks which might reflect an underlying negative attitude on his part. Some physicians, on referring a patient to a psychiatrist, become hostile to the patient. This reaction is often due to the physician's becoming anxious and hostile at his inability to help the neurotic patient he is sending for psychiatric treatment.8 The aforementioned negative attitudes on the physician's part are antitherapeutic and should be assiduously avoided. It is valuable for the referring practitioner to have been in contact with the psychiatrist before the latter sees the patient, and to have communicated to him his somatic and psychologic findings.

If after evaluating the patient's emotional problems the psychiatrist feels that the psychosomatic patient requires and is amenable to intensive psychotherapy, the patient should start psychiatric treatment promptly. The general practitioner or internist should continue to treat the somatic aspects of the case medically, with both physicians collaborating in the total therapeutic regimen, as has been described by one of the authors ^{9, 10} elsewhere. During

acute flare-ups of psychosomatic disorders the patient's medical treatment should be primary, with psychotherapy secondary and essentially supportive. In the more chronic stages of these illnesses, psychotherapy usually is the predominant therapy, medical management staying in the background. general practitioner performs all physical examinations and instrumentations, such as sigmoidoscopy. He prescribes all medication (such as sedatives and narcotics) after consultation with the psychiatrist. In such situations the practitioner should avoid making psychologic interpretations to the patient; he should suggest that the patient discuss his emotional problems with the psychiatrist. On the other hand, as a result of the very personal nature of the psychiatric relationship, the psychiatrist must keep confidential most of the material derived from his psychotherapeutic interviews with the patient. However, it is essential that the psychotherapist keep the internist informed of the general psychologic status of the patient and how his psychiatric treatment is progressing. There should be constant communication and coördination between the psychiatrist and the internist, each physician making his specialized contribution to the whole treatment situation. It is only through this medical-psychiatric collaboration that total treatment of the patient is accomplished.

SUMMARY

It has been estimated that psychosomatic patients make up approximately 50% of the cases seen by the general practitioner and internist. These patients have illnesses in which psychologic disturbances are responsible, wholly or in part, for their diseases. Most of them are treated by the general practitioner or internist, and it is essential that the physician take into consideration, in his total management of the disorder, the patient's psychic as well as his somatic problems. The general practitioner may use various superficial psychotherapeutic technics, such as giving the patient emotional support, affording him an opportunity for ventilation and psychocatharsis, giving him direction and reëducation, manipulating his environment, and at times interpreting certain of his emotional difficulties. The basis of all psychotherapy, superficial as well as intensive, is a warm, positive doctorpatient relationship. The purpose of psychotherapy is to produce a change in the patient's behavior in order to diminish his anxiety and thereby to help his physical condition. If the patient does not respond to this symptomatic management of his illness, he should be referred for a psychiatric consultation. If the psychiatrist feels psychiatric treatment is indicated and the patient is deemed amenable to psychotherapy, the psychiatrist should treat the psychic aspects of the patient's difficulties, and the internist should continue to manage the somatic aspects of the case. From then on, coöperation between the psychiatrist and the internist is necessary to accomplish a comprehensive, total therapeutic approach of the psychosomatic patient. Failure

on the part of the internist to recommend psychiatric collaboration when it is indicated may result in failure of the therapeutic regimen and chronic invalidism for the patient.

SUMMARIO IN INTERLINGUA

Circa 50 pro cento del patientes qui consulta le practico general o le internista ha gravamines somatic de origine complete- o predominantemente psychologic. In le plus grande gruppo de casos de iste genere, il se tracta de disordines psychosomatic que es somatic disordines del visceres precipitate o sustenite primarimente per conflictos emotional. Stress e conflicto emotional produce anxietate, que pare esser le factor responsabile pro le alterationes physiologic con lor consequente pathologic lesiones organic. Iste disordines psychosomatic pote e debe frequentemente esser tractate per le internista qui—in le opinion del autores—es qualificate a attaccar non solmente le factores somatic sed etiam le factores psychic que ha un rolo in le genese de iste conditiones.

In le evalutation medical e le tractamento therapeutic de omne morbo somatic con contributori factores psychogene, il es per consequente importante que le disturbation psychologic es prendite in consideration si ben como le disturbation physic. A parte le detaliate historia medical, le examine physic, e le investigation laboratorial, le internista debe occupar se de determinar le factores psychologic implicate in le declaration e le persistentia del morbo in question. Si il se monstra que le patiente suffre de serie disturbationes psychologic—sin reguardo al severitate de su condition somatic—ille debe esser inviate a un psychiatro pro un evalutation de su stato psychiatric. Si le patiente ha un chronic disordine psychosomatic, si o non il existe un apparente concomitante disordine psychiatric, le autores recommenda un consultation psychiatric, proque tal patientes es quasi semper seriemente disturbate in lor vita psychic, ben que lor conflictos in iste area pote esser celate sub lor symptomas physic. In patientes con morbos psychosomatic de origine recente o con problemas psychologic relativemente superficial, le internista deberea occupar se del factores psychic si ben como somatic.

Le tractamento psychologic que le internista usa pro resolver le problemas emotional de su patiente es designate como psychotherapia superficial. Le technicas usabile in un regime de iste genere include supporto emotional, reconfortation, ventilation e psychocatharsis, redirection e re-education, manipulation del ambiente, e in certe casos interpretation e explication del conflictos del patiente. Le base del psychotherapia es un relation cordial e constructive inter le medico e le patiente. Le objectivo fundamental del psychotherapia in un patiente psychosomatic es effectuar un alteration in le comportamento del patiente pro diminuer su anxietate e assi meliorar su condition physic. Si le patiente non responde a iste regime de psychotherapia superficial per su medico general, ille debe esser referite a un consultation psychiatric. Si le psychiatro opina que un tractamento psychiatric es indicate e si le patiente es considerate como accessibile per un psychotherapia intense, le psychiatro debe tractar le aspectos psychologic del difficultates del patiente e le internista debe continuar le tractamento del aspectos somatic. Postea un intime cooperation inter psychiatro e internista es necessari pro le attacco comprehensive del total problema therapeutic del patiente psychosomatic.

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MULTIPLE MYELOMA: DIAGNOSIS AND MANAGE-MENT IN A SERIES OF 57 CASES *

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MULTIPLE myeloma, once considered an extremely rare disease, has been diagnosed with increasing frequency during the last decade. Whether this has been due to an actual increased incidence or to improved clinical and laboratory recognition is not known. Usually the diagnosis of multiple myeloma is not difficult, but the disease may be at times an obscure and insidious one. Although inevitably fatal, in some cases multiple myeloma may pursue a prolonged and chronic course, and in even the more malignant forms of the disease, chemotherapy and other measures may afford some relief. During the last nine years 57 cases of multiple myeloma have been followed in our clinic. The results of the experience with the diagnostic and therapeutic problems encountered in these patients are reported in this paper.

CLINICAL DATA

Age and Sex. Multiple myeloma is reported to be more common in males than in females. This was true in our series, where the ratio was 1.6:1. Characteristically, the disease occurs in older age groups and is rarely encountered in patients under 30. Only one of our patients was below the age of 40, the vast majority of cases occurring between the fifth

TABLE 1 Clinical Findings in 57 Cases of Multiple Myeloma

Symptoms and Physical Findings		Laboratory Abnormalities	
Pain Weight loss Anorexia, nausea and vomiting Palpable spleen Palpable liver CNS lesions	77% 63% 26% 21% 19% 17.5%	Anemia Elevated ESR Proteinuria Abnormal TP and A/G ratio Elevated NPN Bence Jones proteinuria	91% 82% 61% 55% 34%

X-Ray Abnormalities

Osteolytic lesions	68%
Pathologic fractures	48%
Osteoporosis	35%

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and eighth decades (figure 1). It should be noted that there was no apparent effect of sex or of age at onset on the ultimate length of survival.

Symptoms and Signs

Pain: Pain is one of the most outstanding features of multiple myeloma. It may be classified into three general categories: the boring pain of an expanding lesion in the marrow cavity, the aching pain due to nerve root compression, and the acute, stabbing pain associated with pathologic fractures. Pain is usually severe, but it may vary greatly in intensity and at times may spontaneously disappear. More commonly it is persistent, re-

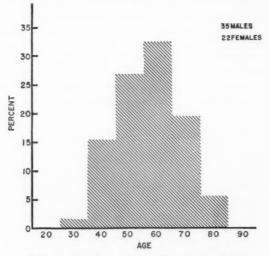


Fig. 1. Distribution by age and sex in 57 cases of multiple myeloma.

quiring frequent administration of narcotics. Back pain due to myelomatous involvement of the spine may present a difficult diagnostic problem. Patients have been treated for herniated intervertebral discs and other allied orthopedic conditions for months before the correct diagnosis has been suggested. In this series, 77% of the patients had pain, usually due to expanding processes in the marrow cavity or nerve root pressure. In two cases the pain was of the aching, periarticular type occasionally described in myeloma.

Weight Loss: Early in the disease the patient may appear to be in good nutrition. However, as the disease progresses profound weight loss and cachexia often develop, simulating other neoplastic conditions. In our series 63% of the patients noted weight loss, ranging from a few to over 50 pounds.

Gastrointestinal Complaints: Anorexia, nausea and vomiting commonly occurred in our patients prior to any therapy. Although more marked in azotemic individuals, the complaints were not necessarily related to renal disease. In spite of the frequency of these complaints, myelomatous lesions were seldom found in the gastrointestinal tract at autopsy.

Neurologic Aspects: Involvement of the central nervous system is not uncommon in myeloma and may result from (1) cord compression due to extramedullary tumor or collapsed vertebra; (2) perineural myelomatous invasion (plasma cytoma); (3) peripheral neuritis, in which there is no apparent invasion of the central nervous system or peripheral nerve with tumor.^{1, 2, 3} In our series there were 10 cases with neurologic lesions, of which eight were due to cord compression. Of these, three developed sudden complete paralysis of the lower extremities due to extramedullary plasmacytomas. In each instance relief was obtained by laminectomy and cord decompression, resulting in complete restoration of function several months postoperatively. In two cases with persistent peripheral neuritis, repeated biopsies failed to reveal any pathologic lesion except nerve atrophy.

Hemorrhagic Tendencies: Although hemorrhagic manifestations have been reported in myeloma, severe hemorrhagic complaints are not common in this disease. In our experience only six patients had bleeding tendencies, and these were limited to minor episodes of epistaxis and mild purpura. While various coagulative defects have been implicated, no consistent abnormalities of the clotting mechanism have been established. Capillary damage, due to abnormal proteins such as cryoglobulin, has undoubtedly been a factor in some cases of abnormal bleeding.⁴

Physical Findings

Physical findings in myeloma are nonspecific and, when present, usually consist of pallor, evidence of debility and at times neurologic signs. Hepatomegaly and splenomegaly have been reported to occur in 10 to 30% of cases. The our series the liver was palpable in 19% and the spleen in 21%. Although obvious tumor masses are uncommon, they are particularly significant, since they may be aspirated or biopsied for diagnostic purposes. While palpable plasmacytomas are reported more commonly by others, \$5, \$6, \$10 in our series there were only three patients with palpable masses, two of these occurring over the chest wall and one over the sternum.

LABORATORY FINDINGS

Peripheral Blood: Anemia, one of the outstanding features of multiple myeloma, occurred in 90% of our cases. Anemia is usually of the normocytic, normochromic variety; it may be mild in degree but often is profound. Three patients in this series presented themselves with hematocrits below 20%. The white blood count is usually not remarkable, the only significant

finding being the occasional presence of myeloma cells in the peripheral blood. With careful search, small numbers of myeloma cells will be found in many cases of multiple myeloma. However, instances where considerable numbers of myeloma cells appear in the peripheral blood are comparatively rare. In this series four individuals were found to have appreciable numbers of these cells in the blood smears, but in two cases this occurred as a terminal event. Several other abnormalities of the peripheral blood are well known, e.g., markedly rapid sedimentation rate, marked rouleau formation, "greasiness," and a peculiar dark blue coloration of the stained smear. These phenomena are associated with the abnormal plasma proteins frequently

found in multiple myeloma.

Bone Marrow: Bone marrow aspiration has proved an invaluable aid in the diagnosis of multiple myeloma. From the standpoint of cytologic detail, several authors have pointed out the superiority of well prepared marrow aspiration smears over histologic sections. 11, 12 Most authorities now agree that the myeloma cell is an abnormal plasma cell.13, 14 Myeloma cells vary in size from a small cell, about 12 µ in diameter, almost identical in appearance to an adult plasma cell, to a large, immature, blastlike cell measuring 20 to 40 \mu. There is also an intermediate sized cell, with a more nearly centrally placed nucleus and less densely arranged chromatin. The cytoplasm of the myeloma cell, stained with Wright's stain, varies from a deep blue to a robin's-egg blue and has a ground-glass appearance. Acidophilic inclusions, called Russell bodies, or clear globules, so-called Mott bodies, may occasionally occupy the cytoplasm. The nucleus of the myeloma cell is usually eccentrically placed and measures from 5 to 7μ in diameter. The more mature nuclei are composed of dense chromatin clumps. However, the "cartwheel" arrangement described in fixed sections is not so characteristic in the bone marrow smears. In more immature cells the nuclear chromatin is spongy, and one or more nucleoli may be present. A perinuclear hof is characteristic of many of these cells, and multinucleated cells are a not uncommon feature.

In myeloma, abnormal cells may constitute from 2% to about 90% of the marrow population. Classically, if the marrow aspiration contains sheets of myeloma cells the diagnosis is unequivocal. With a small per cent of scattered myeloma cells, especially of the more mature cell type, the diagnosis may be less certain. Occasionally, several aspirations from various sites may be necessary before adequate marrow specimens are obtained. In this series the marrow aspiration was diagnostic in 50 of the 57 cases. Surgical biopsy of the bone marrow or tumor masses established the diagnosis in the remaining seven cases.

Serum Proteins: Elevation of the serum proteins, while not pathognomonic of this disease, is a valuable diagnostic clue. Characteristically, the high serum protein is due to marked hyperglobulinemia. However, the total serum protein may be within normal limits, since serum albumin

is frequently markedly reduced. There are a number of other diseases in which an increased total serum protein and hyperglobulinemia may occur, e.g., cirrhosis of the liver, disseminated lupus, sarcoidosis, serum sickness, subacute bacterial endocarditis and miliary tuberculosis. In these conditions there is often an associated plasmacytosis in the bone marrow. While at times it may be difficult to differentiate these diseases from myeloma, careful evaluation of clinical and laboratory findings will establish the correct diagnosis. In our series 55% of the cases showed an elevation of total protein and globulin, whereas only 5% had a normal total protein with high globulin and low albumin.

Abnormal serum globulins are among the most interesting features of multiple myeloma. These globulins are apparently elaborated by the myeloma cell, and various biochemical and biophysical studies indicate their abnormal nature. In a recent publication Putnam 15 has characterized some of these globulins by their physiochemical constants and by their content of N-terminal amino acids. He has concluded that structurally abnormal forms are synthesized in response to this disease, and that physical and chemical differences exist between some of these abnormal globulins. Other investigations have clarified older clinical observations, namely, that patients with multiple myeloma are subject to repeated and severe infections. It is now apparent that susceptibility to infection is due in part to deficient antibody production, as a result of abnormal protein synthesis by myeloma cells. 16, 17 Studies on another characteristic of proteins, namely, their electrophoretic mobility, have shown that the increased globulin in myeloma is usually confined to a remarkably homogeneous component as compared to normal serum or serum with a nonspecific hyperglobulinemia. Several characteristic patterns have been described, i.e., a dense component with the mobility of a slow or fast moving gamma globulin, and a definite component with the mobility of a beta globulin. 18, 19, 20 With the advent of filter paper electrophoresis, this method for the identification of the abnormal serum components has become available to the general hospital. In the last 18 months filter paper electrophoretic studies have been performed on 10 cases in this series. Of these, six showed abnormal gamma and one an abnormal beta pattern. The other three showed no significant abnormality (figures 2 and 3).

Bence Jones Proteinuria: Bence Jones proteinuria, with rare exceptions, is pathognomonic of multiple myeloma. This protein has been reported by various authors ^{5, 9, 10, 21, 22, 23} to occur in from 8% to 87% of cases, and in our series 34% of the patients showed Bence Jones proteinuria. It should be pointed out that recently Putnam ²⁴ has demonstrated at least four different Bence Jones proteins from a physicochemical standpoint. Snapper ⁷ has described a simple and sensitive screening test for determining the presence of Bence Jones protein. This consists of overlaying the urine with a few cubic centimeters of concentrated hydrochloric acid. If no white

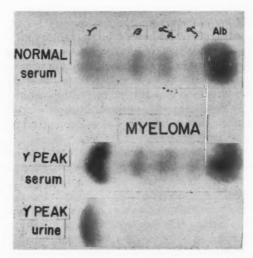


Fig. 2. Filter paper electrophoresis showing abnormal gamma globulin in the serum and urine in a case of multiple myeloma.

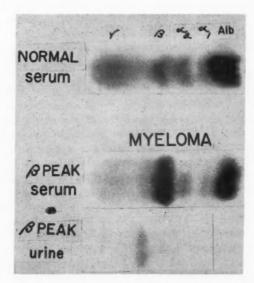


Fig. 3. Filter paper electrophoresis showing abnormal beta globulin in serum and urine in a case of multiple myeloma.

ring is formed at the interphase, Bence Jones proteinuria is not present and no elaborate tests are necessary. If proteinuria is present, various methods may be employed to identify further the abnormal urinary protein. However, in the presence of marked albuminuria, identification of Bence Jones protein may be very difficult. Recently Osserman and Lawlor, using filter paper electrophoresis, have demonstrated a characteristic protein abnormality in the urine of some patients with multiple myeloma. In our series, two of the patients with abnormal serum patterns revealed a protein in the urine with approximately the same mobility as the abnormal serum protein. A third patient, without an electrophoretically abnormal serum protein, showed a concentrated peak of atypical globulin in the urine.

Cryoglobulins: Globulins, which on cooling precipitate and cause the serum to become gel-like, occur in multiple myeloma. At times cryoglobulinemia may be associated with purpuric-like lesions, due to capillary damage in exposed areas of the skin.⁴ While cryoglobulinemia is considered to be a relatively rare phenomenon, in this series five patients had large amounts of cold-precipitable plasma proteins. Probably, with more careful technic, cryoglobulin would be found more commonly.

Roentgenologic Changes in Bone

Several x-ray abnormalities may be found in the bones of patients with multiple myeloma. A classic finding is the punched-out, usually multiple osteolytic lesion, with no evidence of osteoblastic reaction. While the spine, ribs, sternum, clavicle and skull are most frequently involved, any bone may show such lesions. Metastatic cancer or malignant lymphoma may simulate myeloma lesions but usually are associated with some degree of local osteoproliferation. Diffuse osteoporosis, while not pathognomonic, is an outstanding feature of multiple myeloma and must be differentiated at times from post menopausal and senile osteoporosis. Pathologic fractures due to osteolytic or osteoporotic lesions are among the most serious manifestations of the disease and were found in a surprisingly large number of cases in this series. Osteolytic lesions occurred in 68% and pathologic fractures in 48% of the cases. It is worth noting that only five cases in this series were devoid of any of the above bony abnormalities.

Renal Involvement

Severe renal impairment is not uncommon in multiple myeloma. Indeed, in elderly patients with unexplained proteinuria or azotemia, multiple myeloma should always be considered. The renal disease is due to the so-called "myeloma kidney," a lesion characterized by tubular degeneration and atrophy arising from plugs or casts of abnormal globulins in the kidney tubules, as well as from droplets of these proteins in the renal epithelial cells.^{26, 27} Clinically, proteinuria and nitrogen retention were common

findings in our series, with a 61% incidence of proteinuria and a 34% incidence of elevated nonprotein nitrogen. Bence Jones protein, considered pathognomonic of this disease, was present in only 34% of our cases. As pointed out by others, a definite relationship seems to exist between the occurrence of elevated serum globulin and the lack of Bence Jones protein in the urine. On the other hand, in the presence of Bence Jones protein, renal insufficiency, as evidenced by an elevated nonprotein nitrogen, was found in 50% of the cases. When renal disease appears in multiple myeloma, it has been of grave prognostic significance in our experience.

Pathology

A detailed description of the pathology of multiple myeloma is beyond the scope of this paper. However, 27 cases (or 56%) of our patients who died had postmortem examinations. Characteristic and often extensive osteolytic lesions were present in most instances, and in 12 cases there were typical myeloma kidneys. While gross visceral involvement was found in only one case, invasion by small numbers of myeloma cells, especially of the lymph nodes, spleen and liver, occurred in 50% of the cases. In addition to the neoplastic lesions, the presence of amyloidosis and hypercalcinosis has been emphasized by Snapper 7 and others. 28, 29 However, in our 27 autopsied cases, abnormal calcification was not encountered, and amyloidosis was noted in only two cases. In addition to the findings noted at post mortem, local plasmacytomas were encountered in six other individuals in this series. Extramedullary cord tumors were discovered and biopsied at laminectomy in three cases. Plasmacytomas of the chest wall, presenting themselves as solitary tumors, occurred in three patients and were biopsied for diagnostic purposes.

Solitary Myeloma

The existence of "solitary" myeloma has been the subject of much debate. The literature contains unquestionable instances where myelomatous lesions have remained stationary for years. However, in most instances the process, if adequately followed, will demonstrate itself as a disseminated one. In this series, no cases which could be considered as showing solitary lesions were encountered.

TREATMENT

Multiple myeloma is uniquely resistant to all forms of therapy. Except for urethane, no chemotherapeutic agent has been useful. Radioactive P³² has not been beneficial except in rare instances, ^{31, 32, 38} and x-ray, except for localized lesions, has been ineffective. ³⁴ Recently, preparations containing radioactive iodine have been employed, but it is too early to evaluate this form of therapy. ³⁵ In our experience the disease has usually been too dis-

seminated to warrant the use of x-ray therapy. However, in two cases intensive therapy over sites of pathologic fracture was instrumental in relieving pain and promoting bony healing. Stilbamidine is no longer regarded as a useful drug in the treatment of multiple myeloma; indeed, the toxic effect of this drug prohibits its use in this disease. Urethane (ethyl carbamate) has been employed for the last 10 years, and a considerable

number of reports have been published on its use in multiple myeloma. 36-39

In our series an attempt was made to treat practically all cases with this However, only 37 of the 57 cases had an adequate course of urethane therapy. There has been no statistical evidence that urethane has contributed to increased longevity in our patients. Nevertheless, in about 20% of adequately treated patients, urethane produced at least a temporary beneficial effect. Bone pain was alleviated, anemia improved, and in a few cases fall in serum protein and decreased proteinuria occurred. Prolonged remissions which could be attributed to this drug have been rare in our experience. Nevertheless, in three patients who are still living and in relatively good health at this date the disease has been present for over nine years, and all three were treated with large doses of urethane over a 20 to 24 month period during 1947 to 1949. Whether the prolonged course was due to urethane or to the "natural history" of the disease cannot be definitely determined. Another case is of interest in this regard. This patient, a 56 year old man with hyperglobulinemia, transient Bence Iones proteinuria, and a bone marrow containing large numbers of immature myeloma cells, has been on continuous urethane medication (3 gm. daily) since April, 1953. He continues to remain in apparent good health and symptom-free, and carries on normal activities.

In our series, urethane has been administered as enteric-coated tablets: usually 6 gm. a day are given for from three to six days, followed by a maintenance dose of 3 gm. daily. Therapy is continued as long as the patient shows clinical or laboratory improvement, or until some toxic effect precludes further administration. Nausea and vomiting have been the most frequent and disagreeable side-effects of urethane therapy. This has been somewhat overcome by the use of enteric-coated tablets or rectal suppositories. The most serious toxic reaction has been the occurrence of a severe leukopenia, which necessitates the withdrawal of the drug. However, in only three cases in our group was the drug discontinued because of leukopenia. In rare instances, and with large doses of urethane, liver damage may occur; one case in this series apparently died of acute hepatic necrosis. 40 Cortisone or ACTH was employed in 16 of the cases, either alone or with urethane. Little benefit has been observed from steroid therapy; in fact, several patients with severe renal damage developed a rapidly downhill course, perhaps due to the use of these compounds.

In addition to the above measures, management of pathologic fractures, especially of the spine, presents difficult problems. In an effort to keep the

patient ambulatory, back braces or other forms of support should be employed, but there is usually little else that can be offered from an orthopedic standpoint. Blood transfusion is the only treatment for severe anemia and, in the presence of the infections so often encountered in myeloma patients, proper antibiotic therapy should be instituted.

DURATION OF DISEASE

In reports on large series of cases the average survival of patients with multiple myeloma, dated from the onset of symptoms, has been less than two years. ^{5, 6, 7, 9, 21, 41} Since the advent of chemotherapeutic agents the survival time has not been appreciably lengthened. In the series as a whole, the

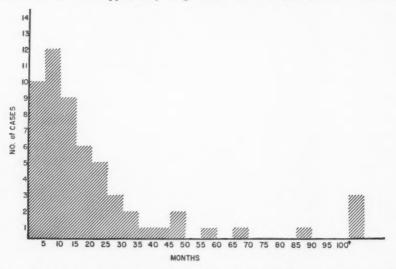


Fig. 4. Length of survival in 57 cases of multiple myeloma, including seven living patients.

average survival was 23.8 months, whereas the median survival was 13 months. The marked discrepancy between the median and the average survival time was due to the fact that three patients survived nine, 11 and 11 years after the onset of symptoms. It should be pointed out that the median survival time of our adequately treated cases was still only 17 months.

Numerous observers have commented on the relation of the degree of maturity of the myeloma cell to the prognosis of the disease. Bayrd ¹⁴ and others ⁶ felt that, in general, the patient with more anaplastic cells had the poorest prognosis. Snapper ⁷ and Lichtenstein and Jaffe ⁴¹ were not convinced that they could estimate prognosis from the nature of the cells. The bone marrow smears from various sites in 50 of our patients were reviewed and classified carefully as to degree of maturity. While three cases with

the most anaplastic cells survived a mean of seven months, the three cases surviving over nine years had mature myeloma cells. However, the remaining cases showed such a discrepancy between cell type and survival that any prognostic statement from cell type alone seems unwarranted.

SUMMARY AND CONCLUSION

Experience with 57 cases of multiple myeloma over the last nine years confirms the fact that this is not an extremely rare disease. The diagnosis is usually not difficult; the presence of pain, anemia and weight loss in an older person, especially if accompanied by unexplained albuminuria, should arouse suspicion of this diagnosis. Physical findings are usually not helpful except for the rare occurrence of palpable tumor masses, and the diagnosis usually depends on laboratory assistance. While rouleau formation, rapid sedimentation rate and elevated serum globulin are highly suggestive, the presence of myeloma cells in bone marrow aspirate, Bence Jones protein in the urine, and the characteristic serum and urine electrophoretic patterns is of special diagnostic significance. It has been pointed out that x-ray evidence of bony abnormalities was present in a high percentage of our cases, and that the presence of osteolytic lesions and pathologic fractures is of particular importance.

At present there is no effective therapy for multiple myeloma. Cortisone or ACTH employed in 16 cases has not been helpful. Local intense x-ray therapy to sites of pathologic fracture resulted in relief of pain and healing of fracture in two cases. Urethane has been used extensively in this series, and approximately 20% of the patients had some benefit from this drug. However, the survival time in this series does not appear to be increased by the use of urethane. It should be noted, however, that four patients who received long-term urethane therapy have apparently undergone prolonged remissions. While it is not certain that this was a direct result of urethane therapy, nevertheless, patients with multiple myeloma should be given an adequate trial with this drug.

ACKNOWLEDGMENT

We are indebted to Dr. Jane Desforges for the electrophoretic studies in this series, and to the physicians who cooperated in making some of the material available to us for study.

SUMMARIO IN INTERLINGUA

Es discutite in iste articulo experientias con 57 casos de myeloma multiple. Le morbo non es extrememente rar. Le diagnose—non infrequentemente inadvertite—es non inusualmente difficile.

Ab le puncto de vista clinic, le presentia, in personas de etate avantiate, de dolores, anemia, perdita de peso, o inexplicate proteinuria deberea inspirar le suspicion de myeloma multiple. Le constatationes physic es usualmente pauco utile, a parte le occurrentias rar de palpabile massas tumoral, e le diagnose debe utilisar le assistentia de methodos laboratorial. Le formation de rouleaus, un sedimentation accelerate,

e elevate nivellos de globulinas seral es constatationes de alte signification suggestive. Tamen, le presentia de cellulas myelomatic in aspirationes de medulla ossee, proteina de Bence-Jones in le urina, e characteristic modos de comportamento electrophoretic del sero es le plus importante criterios diagnostic. Indicationes roentgenologic de anormalitates ossee esseva notate in un alte procentage del casos del presente serie. Le presentia de lesiones osteolytic e fracturas pathologic es particularmente significative.

Al tempore presente, il existe nulle efficace therapia pro myeloma multiple. Cortisona o ACTH esseva usate in 16 casos sin multe successo. Le application local de un intense therapia roentgenologic al sitos de fracturas pathologic resultava in alicun casos in un certe grado de alleviamento. Urethano esseva usate extensemente in iste serie, e circa 20 pro cento del patientes obteneva un certe beneficio ab iste droga. Le superviventia non esseva prolongate per urethano, sed quatro del patientes recipiente longe cursos de urethano ha habite extense remissiones. Ben que il non es certe que le remissiones esseva le effecto del therapia a urethano, patientes con myeloma multiple deberea esser subjicite a adequate administrationes experimental de iste droga.

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ABERRANT PULMONARY ARTERY WITH INTRA-LOBAR SEQUESTRATION *

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This report concerns two examples of a developmental defect of the lungs which is generally considered to be rare. Briefly, it consists of an aberrant pulmonary artery arising from the aorta or one of its major branches, coupled with a dissociated or sequestrated intralobar bronchopulmonary mass. The pulmonary mass is cystic and is usually, but not always, located in the posterior part of a lower lobe. The first of our two cases is an example of this more common type of lower lobe lesion, whereas the second patient represents a variant which is believed to be unique, viz., right upper lobar sequestration with blood supply from the subclavian artery.

The disorder is of interest for several reasons. First, its anatomic consistency appeals to the systemist. Second, there are important surgical aspects, which will be considered shortly. And finally, it is probably far less rare than is generally supposed; interest seems to increase its apparent incidence. Although the first report of the dual anomaly appeared in 1928,¹ the next adequate description was not forthcoming until Pryce's comprehensive study in 1946.² Since then, the total number of reported cases has increased in a geometric fashion to approximately 100.³

MORBID ANATOMY AND DEVELOPMENT

The most widely favored theory of development, that of Pryce,^{2, 4} considers the primary fault to be in the development of the misplaced artery, and the associated pulmonary anomaly to be a complication or secondary effect. Thus, for unknown reasons, blood vessels sometimes differentiate in abnormal locations in the primitive splanchnic plexus of the embryo, locations in which atrophy ordinarily occurs. An aberrant pulmonary artery connecting a dorsal aorta with a developing lung bud is an example of such perverted maturation. With further development and shifts, the artery exerts mechanical effects, presumably traction, on the bud to which it is attached. Where these effects are appropriate, the attached portion of lung becomes dissociated from the parent bronchopulmonary mass and develops in an intralobar position—intralobar sequestration. Certain other

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anomalies, i.e., aberrant arteries with accessory lobe and aberrant arteries to normal lung, are considered by Pryce to be related to this condition, differences in the end result being related to variations in the degree of stress exerted by the artery on its adjoining lung mass.

Apparently this sequence of events is most likely to occur in the region of the septum transversum or primitive diaphragm, with the result that aberrant pulmonary arteries most commonly arise from the lower thoracic or upper abdominal aorta and are intimately associated with the inferior pulmonary ligament. When such a vessel has its origin from the abdominal aorta, it reaches the lung by passing through the diaphragm, either via one of its natural openings or via an accessory hiatus. Anomalous pulmonary arteries less commonly arise from the ascending aorta, innominate artery, celiac axis, intercostal or diaphragmatic vessels and, rarely, from the subclavian arteries.5,6 In the few cases previously reported where the anomalous pulmonary arteries arose from subclavian arteries, no mention has been made of associated sequestration. These arteries may be of systemic type on the aortic side and be pulmonic histologically on the lung side, or they may be predominantly pulmonic or systemic.⁶ Being subject to systemic blood pressure, they frequently undergo atheromatous degeneration.2 In the majority of cases of aberrant arteries with sequestration, venous drainage is by way of the normal pulmonary venous system. Occasionally, however, an anomalous vein accompanies the artery.

These vessels offer definite hazards to the unsuspecting surgeon. They are frequently as large as the renal artery, and several deaths have been reported when they were inadvertently severed.^{7,8,9} The presence of adhesions around the artery and its usual location in the inferior pulmonary ligament, where dissection is difficult and frequently blind, contribute greatly to the surgeon's task.

The associated defect, the sequestrated mass, is incorporated within a pulmonary lobe; the boundaries between it and the normal surrounding lung are poorly defined. Most of them are located in the posterior part of a lower lobe, next to the mediastinum, in proximity to the abnormal artery at its origin. In the few reported cases of upper lobe sequestration, the artery arose from the upper thoracic or innominate artery.⁵ These bronchopulmonary masses consist of varying numbers of cysts and/or dilated bronchi, scanty hypoplastic alveoli, superimposed infection and scar tissue. The bronchi, although usually blind, may have small connections with the normal bronchial tree, permitting entrance of air or opaque oil into the cysts. These communications may be either the result of infection or incomplete dissociation.

CLINICAL ASPECTS

Clinically, the defect may not make itself apparent except by fortuitous radiographic examination. Such silent lesions have been exceptional in

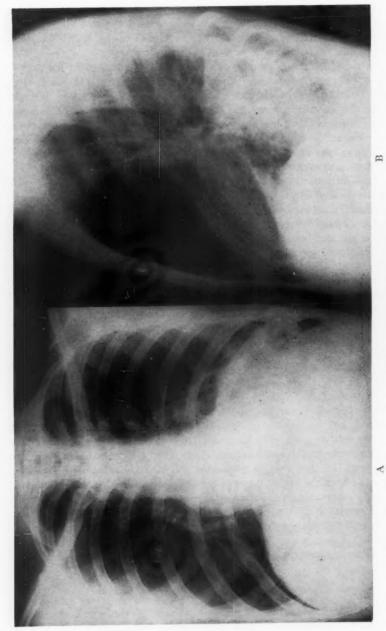


Fig. 1. A. Case 1. Roentgenograms of chest taken January 7, 1955. E.P.A. showing 5 cm., thick-walled cyst in apex of left lower lobe and associated homogeneous density situated medially. B. Left lateral showing lesion lying posteriorly.

reported cases, however, for secondary infection usually produces symptoms at an early age. Hence the condition is frequently diagnosed as recurrent pneumonia, empyema, abscess or bronchiectasis. Chronicity and recurrences eventually dictate the need for surgery. In such situations, particularly in lower lobe masses and cystic lesions, awareness of the possibility of anomalous vessels may prevent serious hemorrhage at operation. Where suspicion was strong, the diagnosis has been established preoperatively with planograms ¹⁰ and aortography. ¹¹

Surgical excision is usually curative.

CASE REPORTS

Case 1. A 21 year old white male was hospitalized at St. Luke's Hospital, Jacksonville, Florida, on January 7, 1955, with a two-week history of fever, malaise and cough, and an eight pound weight loss. There was also a long history of productive cough, a bout of pneumonia in infancy, surgical drainage of left-sided empyema at the age of eight, and "flu" with hemoptysis in 1952. In June, 1954, the patient was rejected for military service because of a "cyst" on the left lung.

Physical examination revealed only a few inspiratory, crackling râles in the left lung base posteriorly. Admission roentgenograms of the chest (figure 1) disclosed a 5 cm., thick-walled, air-containing cystic area in the apex of the left lower lobe and an associated homogeneous density in the posterior basal segment. On bronchography a small amount of dye entered the cyst; none entered the consolidated area, and there was no evidence of bronchiectasis. Bronchoscopy was normal except for moderate narrowing of the left lower lobe bronchus. Under the influence of antibiotics the patient's initial symptoms improved, and a chest roentgenogram taken on January 13, 1955, was felt to show some clearing. Studies for tubercle bacilli were negative.

On January 28, 1955, thoracotomy was performed through a left posterolateral incision. The lower lobe was adherent to the adjacent parietes, diaphragm and mediastinum. It was mobilized and a large artery, measuring 1 cm. in diameter, was found to perforate the dome of the diaphragm and enter the posterior basal segment. The primary hilum contained a normal pulmonary artery and venous system. Lobectomy was performed. On the day after surgery the patient developed uncontrollable shock. The chest was reopened and topical thrombin and numerous small sutures were applied to oozing areas in the chest wall. Subsequently there was a transient pericarditis, which responded to antibiotics. After that the patient became asymptomatic and has remained so until the time of this writing.

Pathologic examination of the left lower lobe and its attached artery showed it to consist largely of a polycystic mass, with dense areas of scar formation, focal abscesses and areas of atelectasis. The largest cyst was 4 cm. in diameter and contained a fibrinous, necrotic debris. Microscopically, the pleura showed numerous highly vascular adhesions. The parenchyma consisted of alternating areas of fetaltype alveoli, lymphoid deposits, masses of fibrous tissue, muscle, rare cartilage formation and focal calcification. The bronchi were markedly dilated; they were lined with nonciliated columnar epithelium in some areas and squamous epithelium in others. The large cyst had a squamous lining. The entire specimen showed a marked increase in vascularity.

Case 2. A 13 year old white male was observed for a six-month period for progressive weight loss and recurrent episodes of hemoptysis, fever, productive cough and chest pain. On occasions he coughed up as much as a cup of blood.

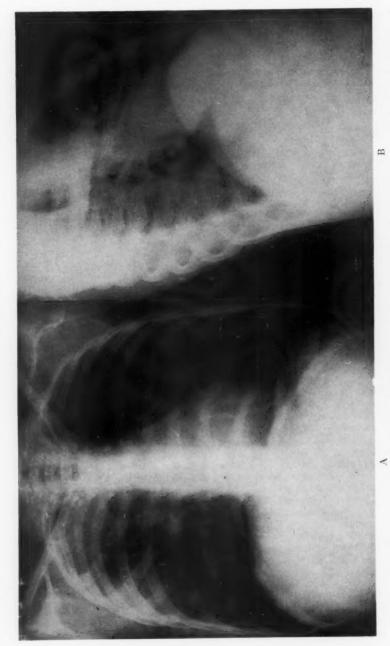


Fig. 2. A. Case 2. Roentgenograms of chest taken April 27, 1955. E.P.A. illustrating an ill-defined, mottled right upper lobe opacity and associated pleural density. B. Right lateral localizing lesion to apex of upper lobe.

During this time numerous studies were performed. The first available chest film, made on April 27, 1955 (figure 2), disclosed a mottled density and considerable associated pleural reaction in the right upper lobe. Skin test with first strength PPD was positive; however, sputum concentrates and cultures, and cultures of gastric aspirates were negative for tubercle bacilli. Bronchoscopy on two occasions revealed only mild erythema of the right upper lobe bronchus. A bronchogram showed absence of filling in the involved area. Serial roentgenograms failed to show change in the lesion.

Because of the patient's failure to respond to various therapeutic measures, and the inability to establish a diagnosis, he was admitted to St. Luke's Hospital, Jacksonville, Florida, on October 13, 1955. Physical examination was normal. On October 28, 1955, a thoracotomy was performed through a right periscapular incision. There were dense adhesions between the upper lobe and the chest wall. Several large arterial trunks connected the diseased apex to the right subclavian artery. They were ligated and lobectomy was performed. The venous drainage of this lobe was via normal channels. The middle lobe failed to expand and was removed but was free of demonstrable disease. After surgery the patient became asymptomatic and remained so, in contrast to the previous state of repeated bouts of respiratory infections and hemoptysis.

On pathologic examination the apex of the right upper lobe consisted of a 5 by 3 by 2.5 cm. fibrous mass which contained numerous dilated hemorrhagic bronchi, cysts and abscesses. There were associated acute and chronic inflammatory changes, extensive fibrosis and a few islands of cartilage. An excessively large number of thickened vessels was present, and the mass was intimately associated with the ligated stumps of the anomalous vessels noted at operation.

DISCUSSION

Our first case, with the anomalous artery arising from the abdominal aorta and supplying a cystic mass in the posterior part of a lower lobe, is typical of the situation as it is usually found, and further discussion would do little more than reiterate material already set forth in comprehensive reviews 2, 8, 4, 5 and briefly summarized earlier in this report. The second case, in whom a sequestrated segment of the right upper lobe was joined to the right subclavian artery by several large trunks, is almost certainly a different variety of the same fundamental defect, differing only in location. We have not found a similar case in the literature. While pulmonary arteries have been previously reported from subclavian vessels, 5, 6, 12 once combined with an accessory lung, 12 no mention has been made of associated sequestration. With Pryce's theory of developmental traction on attached lung in mind, aberrant vessels from subclavian arteries would be expected to be associated with sequestration in some instances, as is seen with pulmonary arteries elsewhere arising from the aorta or its branches. The pattern as it occurred in our second case must be a rarity, then, but it is not inconsistent with theory.

SUMMARIO IN INTERLINGUA

Aberrante arterias pulmonar pote prender lor origine ab le aorta o ab un de su major brancas, i.e. le arteria innominate, le axe celiac, o le vasos diaphragmatic o

subclavian. Lor distribution pote interessar un pulmon normal, lobos accessori, o un cystic massa bronchopulmonar intra le substantia de un lobo pulmonar. Le presente reporto concerne duo exemplos del ultime de iste situationes, i.e. un sequestration intralobar.

In nostre prime caso, un arteria anormal se originava ab le aorta superoabdominal, passava a transverso le diaphragma, e alimentava un massa cystic in le parte posterior del lobo sinistro-inferior. Tal lesiones infero-lobar con provision de sanguine ab le adjacente aorta constitue le majoritate del previemente reportate casos. Le arteria es frequentemente incluse in adhesiones e intimemente associate con le ligamento infero-pulmonar.

In nostre secunde caso, un cystic apice dextere esseva connectite con le adjacente arteria subclavian per plure grande vasos. Iste caso representa un previemente non reportate variante. Ben que arterias anormal ha essite notate que prendeva lor origine in vasos subclavian e occurreva in conjunction con normal pulmon e lobos accessori, nulle association de sequestration intralobar ha unquam essite mentionate.

In le majoritate del casos de sequestration, le drainage venose del anormal tessuto pulmonar occurre via normal canales venose.

Le symptomas es illos de infection secundari, occurrente usualmente in un persona juvene. Le disordine es diagnosticate le plus commumente como pneumonia recurrente, empyema, abscesso, o bronchiectasis. In casos isolate illo ha essite recognoscite ante chirurgia per aortographia e planographia, sed le correcte diagnose es establite le plus communmente in thoracotomia. Considerar le possibilitate de vasos anormal es importante, proque indomitabile hemorrhagias pote resultar si illos es secate accidentalmente. Il es probabile que lor ver incidentia es plus alte que lo que es generalmente supponite. Le excision chirurgic de un segmento sequestrate e su arteria associate resulta in curation.

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THERAPY IN COLLAPSE DUE TO MENINGOCOC-CUS INFECTION *

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Of the many consequences that meningococcal infection can produce, the most fearful is collapse. The multiple changes producing collapse proceed swiftly and with little warning. Unlike the shock attending trauma, hemorrhage or even adrenalectomy, in collapse neither blood and plasma transfusions nor the administration of plasma expanders or electrolyte solutions is of avail in treatment.

There is general familiarity with the acute adrenocortical damage which occurs in this disease. This may be variable in its degree and reversibility. The ultimate is, of course, obliterating hemorrhage. Regardless of severity, the insult to the adrenal cortex occurs precisely when demands of severe stress upon the gland for its product are greatest. Also, there is overwhelming toxicity. Bacterial toxin may produce widespread vascular changes and uncompensated expansion of vascular capacity. Consequent relative reduction in effective blood volume ensues. Dehydration is frequent and may be severe. We know that death follows quickly upon these changes, so that, at the outset, ideal therapy combines steps toward quick elimination of meningococci with measures designed to sustain life while the former act.

ANTIBACTERIAL THERAPY

Basic in eliminating the hazard of shock is elimination of the meningococcus. Sulfonamides remain the agent of choice ⁵ but, because of the delay of several hours before maximal antimeningococcal effect is achieved, penicillin, with its more immediate though less decisive effect, is combined.⁶

METHOD

In the cases treated at this hospital, sulfonamides in the form of sulfadiazine or Gantrisin have been used. Five grams of sodium sulfadiazine or 4 gm. Gantrisin were given intravenously initially, followed by 2.5 gm. of the former or 2 gm. of the latter every 12 hours. When the patient could tolerate oral therapy, either of the above drugs was administered by mouth, 1 gm. orally every four hours. This was continued a minimum of 14 days, or for 72 hours after the patient became afebrile.

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During the acute phase of the infection crystalline penicillin-G was given in the usual large doses, 1,000,000 units every two hours intramuscularly. Following the seriously ill phase, the use of penicillin varied. In many the dosage was reduced sharply, and in some the drug was abandoned.

During the four years preceding July, 1954, 63 patients, five of whom were admitted with the Waterhouse-Friderichsen syndrome, were treated for acute meningococcal infection with this antibacterial regimen. Despite adequate antimicrobial therapy and resourceful support (available agents including DOCA, cortisone, ACTH, norepinephrine, adrenalin in oil, plasma albumin and Coramine were used at various times), one patient with Waterhouse-Friderichsen syndrome died. One other patient developed the syndrome while under treatment and died, and three progressed from mild toxemia and hypotension to severe shock. Of these, one died as a direct result of collapse with adrenal hemorrhages, and another died of massive gastrointestinal bleeding, with associated bilateral adrenal hemorrhage found at autopsy.

STEROID THERAPY

Effective use of cortisone in the Waterhouse-Friderichsen syndrome was reported by Nelson and Goldstein in 1950.⁷ Since then, frequent reports of such successful therapy have appeared. In 1953 Kinsell advocated and reported success with administration of adrenocortical steroids at the outset in every case of meningococcic meningitis.⁸ Since July, 1954, we have employed similar measures in addition to the described antibacterial regimen in the treatment of our predominantly young adult cases.

METHOD

Hydrocortisone was given intravenously by continuous administration at the rate of 300 mg. per 24 hours to all patients with meningococcal meningitis and/or meningococcemia. This was continued as long as there appeared to be any danger of insult to the adrenal cortex by virtue of sepsis. With return of the temperature toward normal, cessation in formation of cutaneous lesions, return of consciousness and strength and stabilization of blood pressure, cortisone by oral or intramuscular route was substituted. The dosage was then tapered gradually to prevent "rebound" phenomena and to exclude the possibility that exogenous steroid had masked significant adrenocortical destruction.

With this plan in effect we have treated 17 cases without an instance of collapse developing under therapy. Among these were seven patients in whom the infection was localized to the meninges and seemed to remain so throughout the course. Ten patients evidenced extensive petechial rashes, coalescing hemorrhages or ecchymoses, plus positive cultures of blood or skin lesions for *Neisseria intracellularis* Type II or IIA.

One other patient (case 1) died. He was not treated in the usual way. Because of a history of hypertension, occurrence of oliguria and progressive nitrogen retention, hydrocortisone was withheld at first and sulfadiazine was discontinued early in the course. While severe meningococcal infection was present, several major disease entities apparently conspired in his death.

PRESSOR AMINES

Even combined hormonal-antimicrobial therapy may be inadequate once shock is established. The most successful immediate emergency measure to counter collapse in these cases has been the administration of pressor amine substances.^{9, 10, 11}

Three other patients (cases 2, 3 and 4) were admitted to our care in shock. In addition to the steps outlined above, 4 to 8 mg. 1-norepinephrine in 1,000 c.c. of fluid proved an effective intravenous medication in returning blood pressure levels to normal and, by continued administration, maintaining them for at least a short time.

FLUID AND ELECTROLYTES

The necessity for close observation, correction and maintenance of fluid and electrolyte balances is obvious in this type of disease—doubly so, of course, in patients under steroid therapy. In our cases no marked deviation from normal ranges of blood chemistry was observed except in case 1.

CASE REPORTS

Case 1. A male, 18 years old, known to have had an elevated blood pressure for two years, was hospitalized for a week because of sore throat. He felt well the day after discharge but the following day awoke with edema of the face and ankles, and passed red urine. He was brought directly to the hospital from his barracks because he appeared to be seriously ill. When first seen he was lethargic and had edema of the face and ankles. His temperature was 101° F. The mucous membranes were dry. He had a generalized petechial rash and a stiff neck. Blood pressure was 140/80 mm. of Hg. A small amount of urine obtained by catheter was grossly bloody. Lumbar puncture revealed pus cells, and a positive culture for meningococci was obtained. He received sulfadiazine and penicillin therapy as outlined. Six hours after admission he developed acute left ventricular failure and peripheral vascular collapse. Hydrocortisone administration was then begun, and he was digitalized intravenously with Cedilanid. The patient was afebrile within eight hours. Pulmonary edema cleared and blood pressure returned quickly to admission levels. Because the urinary output was less than 50 c.c. in the first 24 hours, the sulfonamide was discontinued. The following day the entire right lung presented evidence of consolidation, both clinically and by x-ray. New ecchymoses continued to form. The third day the patient passed a copious tarry stool. Evidence of consolidation extended to the left lower lobe and a steadily rising nonprotein nitrogen with continuing oliguria were observed. Anticatabolic therapy was instituted, together with strict control of fluid replacement. Streptomycin, 1 gm. every eight hours, was begun. On the fourth day diuresis began, with large amounts of urine of low specific gravity containing heavy albumin and many red cells. Nonetheless, his course continued rapidly downward and evidence of progressive pulmonary consolidation continued. He died suddenly the morning of the fifth hospital day.

The following findings were made at autopsy:

Acute glomerulonephritis; left ventricular hypertrophy (the heart weighing 550 gm.), with acute right ventricular dilatation and focal interstitial myocarditis; hemorrhagic pulmonary edema with hyaline membranes lining the alveolar walls on microscopic examination; resolving meningitis with negative bacteriologic studies, and generalized anasarca.

Case 2. A male of 19 years was admitted to the hospital with symptoms of headache and lethargy for 24 hours. He presented with mental confusion, a stiff neck and positive Kernig's sign. There were generalized petechial hemorrhages. The blood pressure was 60/0 mm. of Hg. Blood and spinal fluid cultures were positive for Neisseria intracellularis. In addition to hormone-antimicrobial therapy as described, 1-norepinephrine was given, with immediate response. Following this the blood pressure remained stable. The patient became afebrile on the ninth hospital day. Fever recurred later but ceased following retreatment with sulfadiazine.

Case 3. A 17 year old male, who was admitted because of malaise, developed headache and stupor, finally becoming semicomatose. Nuchal rigidity and Kernig's sign were present, and the blood pressure fell to 70/40 mm. of Hg, with generalized petechial hemorrhages developing. Spinal fluid revealed pleocytosis, and culture for Neisseria intracellularis was positive. The patient received the outlined therapy, including 1-norepinephrine intravenously, which was required for 60 hours before the blood pressure maintained itself at satisfactory levels. Fever became normal

and by the third hospital day the patient was symptom-free.

Case 4. An 18 year old male was admitted to the hospital six hours after he had begun to complain of headache. Before he could be transported from his barracks to the hospital he became comatose. On admission he could not be aroused, and dependent lividity was present. The skin was cold. There was no obtainable blood pressure, and respirations were imperceptible. Heart tones, however, persisted. Four milligrams of 1-norepinephrine were given rapidly intravenously. Hydrocortisone, penicillin and sulfadiazine were also begun at once in the manner described. Within five minutes detectable blood pressure was obtained, and within 20 minutes blood pressures exceeding 100 systolic could be obtained. The patient regained consciousness during the first six hours of his hospital stay and became afebrile subsequently. 1-Norepinephrine therapy had to be continued for the following 36 hours. Hydrocortisone was continued seven days, following which oral cortisone was administered and gradually withdrawn, without ill effects. His remaining hospital course was unremarkable except that the large ecchymoses which had developed during the first 48 hours later ulcerated and required several months to heal. Subsequently, measurement of adrenocortical activity was normal in all respects and the patient returned to duty.

DISCUSSION

Experiences in therapy of 84 sporadic cases with acute meningococcal disease, while demonstrating the well known efficacy of sulfonamides and penicillin, seem to reveal that greater aid in the preservation of homeostasis can be obtained with immediate administration of rapidly acting intravenous hydrocortisone, even in those cases where obvious collapse and/or sepsis are not present. Hydrocortisone may be more desirable than cortisone because of its more direct metabolic effect. The essential step is to produce a level of circulating hormone so rapidly that it is available in event of any adreno-

cortical damage. In addition to this, the anti-inflammatory or antitoxic effects ^{8, 12} of this substance are also important in reducing the lethal potentialities of the disease. If, in retrospect, steroid should prove to have been unnecessary, the small amount given for so short a time would cause little if any harm, especially in the usually young, previously healthy patient who is subject to this disease.

Once collapse has occurred, steroid-antibiotic therapy alone may be inadequate. Here the pressor amines find specific usefulness. One such drug should be available for immediate use in any facility where treatment of such cases is anticipated. With these the patient admitted to treatment in shock may be sustained sufficiently that the former specific remedies may have adequate opportunity. While their use alone may have certain failings, the combination of 1-norepinephrine and steroids seems to be synergistic in reversing collapse. 11

Experience with epidemic types of meningococcal organisms may require some revisions or reveal flaws in this regimen. The new, more potent, more specifically "anti-inflammatory" steroids have yet to be evaluated. We believe, nonetheless, that the mode of therapy presented here has combined the most significant advances in the treatment of acute meningococcal infection to the best possible advantage.

SUMMARY AND CONCLUSIONS

The danger of acute collapse exists in every case of acute meningococcal infection. Successful treatment requires immediate institution of adequate antimicrobial therapy, the most satisfactory being a combination of sulfon-amide and penicillin by available routes, with anticipation of adrenocortical failure and overwhelming toxemia by immediate administration of hydrocortisone in every case. Eighteen patients treated in this manner did not develop collapse following admission to the hospital. 1-Norepinephrine treatment of collapse (if it occurs before specific therapy has succeeded) has proved life-saving. Three additional cases admitted in collapse were saved in this way.

A combination of effective measures is discussed and recommended.

ACKNOWLEDGMENT

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SUMMARIO IN INTERLINGUA

Le periculo de acute collapso circulatori existe in omne caso de acute infection meningococcal. Le tractamento efficace require le institution immediate de un adequate therapia antimicrobial. Le plus satisfactori es un combination de sulfonamido con penicillina administrate per le vias que es disponibile. Es presentate un programma de prophylaxe contra disfallimento adrenocortical e toxemia fulminante per le administration precautionari de hydrocortisona in omne casos del typo discutite. Dece-octo patientes tractate in iste maniera escappava al syndrome de Waterhouse-Friderichsen post lor admission al hospital. Le uso de aminas pressori se ha provate capace a salvar le vita del patiente in casos in que le collapso occurreva ante que le therapia specific habeva devenite active. In iste maniera tres patientes esseva salvate ben que illes arrivava al hospital in stato de choc.

Le comparation del resultatos obtenite in 21 patientes tractate secundo iste programma con le resultatos in 63 casos tractate secundo methodos de character plus conventional es multo favorabile con respecto al statistica de morbidate e mortalitate.

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SERUM TRANSAMINASE IN PULMONARY DISEASE AND MULTIPLE INFARCTIONS *

By JOHN R. WALSH, M.D., FRED L. HUMOLLER, Ph.D., and Frederick G. Gillick, M.D., F.A.C.P., Omaha, Nebraska

In 1954 LaDue and collaborators 1 reported on the value of the serum transaminase (SGO-T) level as a diagnostic measure for acute myocardial infarction. Since that time this test has become as popular as the electrocardiogram in studies of patients suspected of this disorder. Elevations of the SGO-T have been found in a high percentage of patients with acute myocardial infarction.²⁻⁴ It was anticipated that this test would provide a method for differentiating myocardial infarction from disorders simulating it, such as pancreatitis, pulmonary infarction and coronary insufficiency. However, subsequent studies have indicated that the SGO-T test is less specific than was originally believed. Increased values have been found in cases of hepatic necrosis, 3, 5-7 obstructive jaundice, 3, 5 pancreatitis, 8-8 rheumatic myocarditis and renal infarction.2, 10 While the SGO-T is still of great value as a diagnostic method for myocardial infarction, it may also furnish useful information in other diseases, particularly those affecting the liver.

The basis for the acceptance of the serum transaminase activity as a measure of myocardial infarction was established by animal experimentation, which revealed extremely high concentrations of transaminase in heart muscle as compared with that in skeletal muscle, liver, kidney and brain. 11, 12 The present study, while confirming previous observations in myocardial infarction, also reveals that one can observe a rapid increase and an equally rapid decline of SGO-T activity in conditions other than myocardial infarction. Further, an increased SGO-T value in patients with pulmonary disease is considered to be worth reporting.

PROCEDURE

In the present study 318 determinations of SGO-T activity were carried out on 112 hospital patients. Of these, clinical and electrocardiographic or autopsy evidence of myocardial infarction was present in 50 patients.

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istration Hospital, 4104 Woolworth Avenue, Omaha 5, Nebraska.

In addition, SGO-T values were obtained in various diseases, as shown in figures 1 and 3 and in table 1.

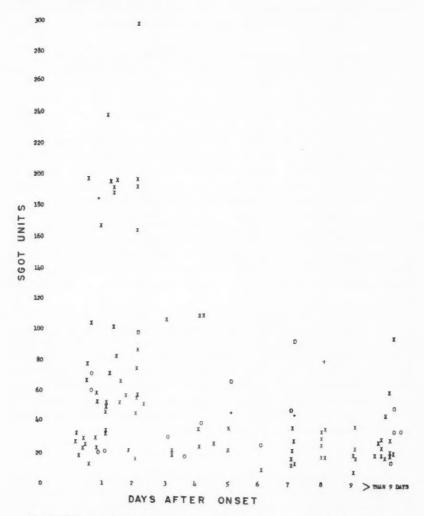


Fig. 1. Time relationship of serum transaminase levels in patients with myocardial infarction (x), pulmonary infarction (o) and pneumonia (+).

SGO-T determinations were carried out by the spectrophotometric method of Karmen et al.,13 and the results are expressed in the units proposed by these authors.

TABLE 1
Elevated SGO-T in Miscellaneous Conditions*

Patient	SGO-T	Diagnosis
A. D.	668-202	Pulmonary and renal infarction
P. G.	74	Trauma to chest
D. D.	58	Trauma to arm
A. L.	92-68	Hematoma of leg
Mc. C.	81	Acute pancreatitis
F. W.	70-92	Metastatic carcinoma (liver)
	58-52	,
I. M.	48	Pancreatic carcinoma
G. P.	118	Cirrhosis of liver
C. T.	128	Uremia
J. B.	44	Penicillin reaction

^{*} See also figure 3.

RESULTS

The SGO-T activity in various diseases is shown in table 1 and figure 1. The SGO-T level obtained in normal individuals (hospital personnel and medical students) was found to be 19.5 ± 3.9 units. However, for comparative evaluation of clinical data the following ranges have been arbitrarily adopted in this hospital:

Normal range Abnormal but nondiagnostic range 40 units 40 to 100 units Abnormal and diagnostic range 100 units

In coronary artery disease only patients with myocardial infarction and, in four instances, patients with clinical and electrocardiographic patterns of coronary insufficiency gave abnormal results. It is probable that necrosis of cardiac muscle occurred in the four latter instances, since the distinction between myocardial infarction and coronary insufficiency is often difficult. The range of increased levels in myocardial infarction was 46 to 299 units.

The distribution of SGO-T values in myocardial infarction is illustrated in figure 1. Several important features deserve comment. As has been previously described,1-4 the rise in SGO-T begins six to 12 hours after the onset of myocardial infarction and, except for a few instances, all elevated values are seen in the interval between six hours and four days. An occasional elevation is shown in 10 to 14 days following myocardial infarction, suggesting that there was an extension of the infarction. Figure 2 illustrates such a case, in which clinical and electrocardiographic data were consistent with this course. Unfortunately, determinations were not done often enough in these instances to demonstrate whether a secondary elevation occurred, as described by LaDue and Wroblewski,2 or persistent elevation ensued. Figure 1 clearly points out that normal values in this disease are to be expected if the determination is done on specimens obtained after the fifth or sixth day, or in the first few hours after the onset of infarction. A typical example of the latter was seen in one of the hospital personnel, whose transaminase value two and one half hours after the onset

of pain was 20 units. The electrocardiogram revealed an acute posterior myocardial infarction, confirmed at autopsy by a recent thrombus completely occluding the left circumflex coronary artery.

In figure 1, several normal values are observed between 12 hours and four days. A few of these may be explained by the indefinite onset of symptoms in some patients, so that the time interval may be questionable. In a few instances an earlier value had been elevated, so that the normal value represents an early decline in the SGO-T.

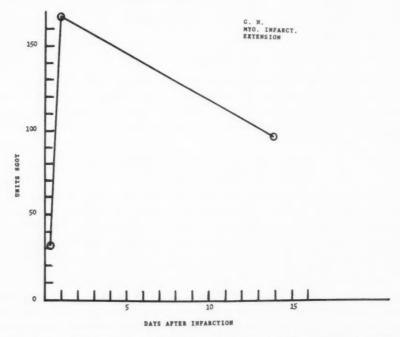


Fig. 2. Persistent elevation of SGO-T, suggesting extension of myocardial infarction.

Figure 1 also shows the distribution of SGO-T in pulmonary disease. While most values are within normal limits, elevations between 40 and 100 occur in pulmonary infarction, especially after the fourth day. While increased values are uncommon in the "myocardial infarction area" (six hours to five days), they occur often enough to suggest that the test cannot be used to differentiate myocardial from pulmonary infarction. However, it is rare for values to exceed 100 units in pulmonary disease; thus, a value of 186 units was found in one patient with fulminating pneumonia, and another patient with pulmonary infarction had 104 units. In the present study, values greater than 40 units were obtained in such diseases as pulmonary

infarction, multiple infarctions, pneumonia, carcinoma of the liver, pancreatitis, trauma and cirrhosis, and in one patient with uremia (table 1).

The highest SGO-T values were found in patients with multiple infarcts. As shown in figure 3 and table 1, patients with multiple pulmonary and renal infarcts showed an SGO-T activity of 500 units or more. These findings are in agreement with the observation of Agress et al. 4 that in cases of experimental myocardial infarction the SGO-T level is a direct function

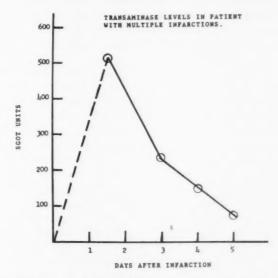


Fig. 3. Serum transaminase levels in multiple pulmonary and renal infarctions, showing time sequence similar to that obtained in myocardial infarction.

of the amount of tissue undergoing necrosis. Figure 3 shows the results obtained when periodic SGO-T levels are determined in a case of multiple infarctions. The shape of the curve obtained when SGO-T levels are plotted against time after onset is strikingly similar to that found in myocardial infarction. At autopsy, multiple pulmonary infarcts as well as a renal infarct were found.

While many values for myocardial infarction fell in the range from 40 to 100, other miscellaneous conditions (table 1) gave similar values. Since these conditions are numerous and diverse, they are not considered diagnostic for any specific disease.

DISCUSSION

The present study was undertaken to determine the specificity of SGO-T determination for myocardial infarction. Previous investigators have

stressed the fact that, in this disease, not only are very high SGO-T values obtained, but also when the time course of the SGO-T level is plotted a typical curve is obtained. It has been shown in human patients as well as in experimental animals that diseases other than those involving the myocardium can give high SGO-T levels. The present investigation shows that the typical curve for the time course of SGO-T levels of myocardial infarction can be observed in human patients in the absence of myocardial involvement (figure 3). These observations suggest that SGO-T levels must be interpreted with considerable care and that they are not by themselves diagnostic of myocardial infarction.

The finding of increased SGO-T activity in other diseases should not be interpreted to mean that it has no value in myocardial infarction. An increased level is found in most instances of myocardial infarction when the serum is obtained at the appropriate time. When evaluated with the clinical picture and correlated with the electrocardiogram, it contributes supportive evidence for a diagnosis, especially with values over 100 units.

Rarely, a normal SGO-T occurs with acute myocardial infarction (figure 1), and such a value, even when the samples are taken at the proper time, does not therefore exclude the diagnosis.³ On the other hand, when the transaminase values are normal, the specimen usually has been taken too early, before the release of transaminase from the necrotic tissue, or too late in the course of the disease, after the transaminase level had returned to normal. When an increased SGO-T is seen over a prolonged period in myocardial infarction it may lead one to suspect that an extension of the infarction has occurred, as is demonstrated in figure 2. Clinical and electrocardiographic evidence is consistent with this impression.

Increased values of SGO-T in pulmonary disease, and especially in pulmonary infarction, have not been stressed by previous investigators. Most observers report normal values in pulmonary infarction. Stroke and associates, however, found abnormal values in eight of 15 patients, the rise in values appearing later than that seen in myocardial infarction. Our results tend to confirm their findings but show occasional elevated values in the "myocardial infarction zone." However, values rarely exceed 100 units.

Abnormal values in pancreatitis, cirrhosis of the liver, carcinoma of the liver and trauma have been reported more extensively by other observers. 3, 5-7 The increased level found in one patient with uremia is unexplained even after autopsy. Normal values have previously been stressed in this situation. It has been stated 3 that the normal route of excretion of transaminase is through the biliary system. The possibility that the elevated value in uremia may be related to myocardial or pericardial involvement must be considered, since elevated values have been found in rheumatic carditis. 9

SUMMARY

While increased SGO-T levels are found most commonly in acute myocardial infarction, elevated levels are found often enough in necrosis and infarction of other organs to suggest caution in interpretation. Curves of the same configuration as that obtained with myocardial infarction can be obtained in other situations, as is illustrated in patients with multiple infarctions. Increased SGO-T levels can be found in pulmonary disease, but usually occur later than with myocardial infarction. Levels above 100 units are more suggestive of myocardial infarction. However, elevated SGO-T values are occasionally found in pulmonary disease in the "myocardial infarction zone."

SUMMARIO IN INTERLINGUA

In iste studio 318 determinationes del transaminase glutamic-oxalacetic del sero (T-GOS) esseva effectuate per le methodo spectrophotometric de Karmen in 112 patientes hospitalisate con le objectivo de determinar le specificitate del methodo pro infarcimento myocardial. Le datos confirma le previemente reportate augmento de T-GOS inter sex horas e quatro dies post le declaration del infarcimento myocardial. In sporadic casos, elevationes esseva observate 10 a 14 dies post le infarcimento myocardial. Isto pareva indicar le occurrentia de un extension del infarcimento.

Durante que augmentate nivellos de T-GOS es trovate le plus communmente in acute infarcimento myocardial, illos occurre etiam non infrequentemente in necrosis a infarcimento de altere organos, de maniera que lor interpretation debe esser effectuate con grande circumspection. Le plus alte valores de T-GOS esseva trovate in patientes con multiple infarctos pulmonar e renal. In tal casos, nivellos de 500 unitates e plus esseva observate. Le curvas del nivellos de T-GOS como function del tempore post le declaration del infarcimento esseva alora frappantemente simile al correspondente curvas obtenite in casos de infarcimento myocardial. In infarcimento pulmonar, elevationes de inter 40 e 100 unitates pote occurrer, specialmente post le quarte die. Tamen, in certe casos le augmentate nivellos se manifesta durante le intervallo inter le sexte hora e le quinte die, i.e. exactemente como in casos de infarcimento myocardial. Iste facto reduce evidentemente le utilitate del test pro le differentiation inter infarcimento myocardial e infarcimento pulmonar. Tamen, le occurrentia de valores de plus que 100 unitates in morbo pulmonar es rar. Le presente serie includeva solmente duo casos de iste genere. Un valor de 186 unitates esseva registrate in un patiente con pneumonia fulminante e un valor de 104 unitates in un patiente con infarcimento pulmonar. Le studio revelava pro T-GOS valores de plus que 40 unitates in morbos como in farcimento pulmonar, infarcimentos multiple, pneumonia, carcinoma del hepate, pancreatitis, trauma e cirrhosis del hepate, e in un caso de uremia.

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THE L. E. PHENOMENON IN RHEUMATOID **ARTHRITIS** *

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THE specificity of the lupus erythematosus phenomenon for the diagnosis of systemic lupus erythematosus has been emphasized by many investigators.1-7 Nevertheless, occasional reports continue to appear describing this phenomenon in diseases other than systemic lupus erythematosus. Positive reactions have been reported in isolated cases of periarteritis nodosa,8 thrombotic thrombocytopenic purpura,9 tuberculosis 10, 11 and postnecrotic cirrhosis. 12, 13 The phenomenon has been reported after hypersensitivity reactions to penicillin,14,15 tetanus antitoxin,16 phenylbutazone 17 and following the administration of hydralazine 18, 19, 20 and prolonged steroid therapy.21, 22 The presence of L. E. cells has been mentioned but not thoroughly differentiated from nucleophagocytosis in isolated cases of multiple myeloma, 23 pernicious anemia, 24 leukemia 25 and dermatitis herpetiformis. 24 The evidence suggests, therefore, that the L. E. phenomenon may be observed in diseases other than systemic lupus erythematosus.

The relationship of systemic lupus erythematosus to rheumatoid arthritis has attracted considerable attention. Table 1 summarizes the incidence of articular manifestations in patients with systemic lupus erythematosus indistinguishable from those of rheumatoid arthritis. Table 2 summarizes the incidence of positive L. E. tests in patients with rheumatoid arthritis as reported by various authors. The interpretation of these findings is varied. The authors listed in table 1 regarded the joint changes as part of the clinical picture of systemic lupus erythematosus. Of the authors in table 2, Ishmael 35 thought it significant that the majority of his patients with rheumatoid arthritis exhibiting the L. E. phenomenon were on steroid therapy at the

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Table 1

Cases of Systemic Lupus Erythematosus with Joint Changes Indistinguishable from Those of Rheumatoid Arthritis

Authors	Year	Number of Cases of S. L. E.	Number and Per Cent of Cases with R. A. Change (Joint Deformities)
Baehr, Klemperer, Schifrin ²⁶	1935	23	2 (8.7%)
Reifenstein et al.27	1939	17	3 (17.6%)
Shearn and Pirofsky ²⁸	1952	34	4 (12%)
Ross and Wells ^a	1953	34	9 (28%)
Jessar et al.4	1953	44	15 (34%)
Friedman et al.29	1953	13	5 (38%)
Dubois ⁶	1953	62	19 (30.6%)
Gold and Gowing ³⁰	1953	26	4 (15%)
Harvey et al.5	1954	138	28 (20%)
Haserick ³¹	1955	126	Considered rare
Mikkelsen et al. ⁸²	1955	21	5 (24%)

time of testing. Hijmans and associates ^{33a} considered two possible explanations for the L. E. phenomenon in rheumatoid arthritis: first, that these cases may represent a chronic form of systemic lupus erythematosus; second, that the phenomenon may represent a nonspecific reaction in patients with rheumatoid arthritis. Ross and Clardy ³⁷ found that the L. E. phenomenon occurred in patients with a higher incidence of multisystemic involvement.

It was the purpose of this study to determine the incidence and specificity of the L. E. test in patients with rheumatoid arthritis. Furthermore, efforts were made, after comprehensive studies, to determine common denominators in patients with a positive L. E. test.

THE L. E. PHENOMENON

Method: The L. E. test was performed in 91 patients with rheumatoid arthritis. The first 50 cases were studied by the oxalate, heparin and clot technics, the latter being a modification of the two-hour Zimmer clot preparation. The oxalate or heparin methods of L. E. preparation were found to

Table 2
Incidence of Positive L. E. Tests in Patients with Rheumatoid Arthritis

Authors	Year	Number of Cases Tested	Number and Per Cent of Positive L. E. Tests
Haserick ²	1951	13	0
Walsh and Egan ¹	1952	5	0
Dubois ⁶	1953	18	0
Harvey et al.5	1954	116	0
Hijmans et al.88a	1955	455	54 (12%)
McCov et al.34	1955	80	20 (25%)
Ishmael et al.35	1955	520	15 (3%)
Ogryzlo ¹⁷	1955	114	9 (8%)
Weiss and Swift ³⁶	1955	46	5 (10%)
Ross and Clardy ⁸⁷	1956	91	18 (20%)
Kievits et al. 33 b	1956	488	81 (17%)
Present study	1956	91	25 (27%)

be comparatively insensitive, and therefore only the clot method was used after the first 50 cases. The May-Grünwald-Giemsa stain produced a more vivid color of the amorphous mass in the L. E. cells and facilitated their identification. Only those preparations revealing smoky, purplish, homogeneous, amorphous masses in the L. E. cells were considered positive.

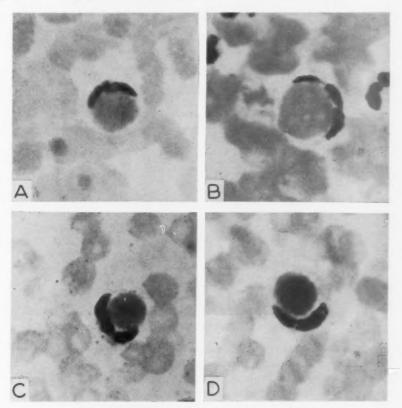


Fig. 1. Typical L. E. cells in four positive patients.

The slides and 50 negative controls were studied as unknowns by two of the authors. Each slide was examined for a minimum of 15 minutes before being declared negative. All of the positive preparations were stained by the methyl green ³⁹ and Feulgen ⁴⁰ technics to confirm the presence of depolymerized desoxyribosenucleic acid, and to differentiate these cells from tart cells and cells showing nucleophagocytosis. Examples of positive preparations as well as examples of nucleophagocytosis and tart cells are shown in figures 1 and 2. When the latter were observed in the absence of L. E. cells, repeated examinations revealed a positive test in eight cases.

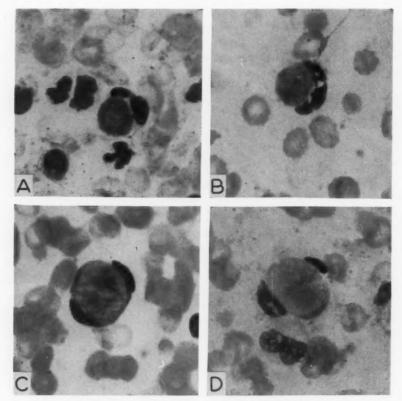


Fig. 2. Nucleophagocytosis as seen in several patients.

An attempt was made to grade the ease with which L. E. cells could be found. This was difficult, since the number per field varied markedly in the same slide or in several slides made at the same time. In general, however, three groups could be distinguished on search with the low power: (1) a strongly positive group, in which numerous L. E. cells were immediately seen; (2) a moderately positive group, in which cells could be found with ease, and (3) a weakly positive group, in which careful search was required to find typical L. E. cells.

Results: Following this procedure, positive L. E. preparations were found in 25 of the 91 patients. Fourteen were strongly positive, eight were moderately positive, and only three were weakly positive.

CLINICAL FEATURES

A total of 91 patients with typical rheumatoid arthritis was studied. Twenty-nine were obtained from a Veterans Administration hospital, 10 from a large general hospital and anemia clinic, and 52 from a chronic disease hospital. The patients were divided, on the basis of the L. E. test, into a positive group and a negative group. A comparison of clinical and laboratory findings in the two groups is presented in tables 3 and 4.

Forty-six of the patients were men and 45 women. The high incidence of men is due to the partial selection of cases from a veterans hospital. Thirteen males and 12 females had positive L. E. preparations. At the time of study approximately two thirds of both the positive and the negative

TABLE 3

TABLE 0	Number of	Cases (91)
	_	
	Positive (25)	Negative (66)
Sex Distribution		
Male Female	13 12	33 33
Age in Years		
20–29 30–39 40–49 50–59 60–69 70 and above	0 2 5 7 10	5 11 6 15 21 8
*Duration of Disease in Years		
0- 5 6-10 11-15 16-20 21 and over	2 5 8 5 4	15 10 12 19
Type of Disease		
Peripheral Spondylitis "Combined"	18 0 7	43 11 12
Stage of Disease (Peripheral or combined with peripheral predominating)		
Stage 1 Stage 2 Stage 3 Stage 4	0 1 7 14	0 11 12 25
Stage of Disease (Spondylitis or combined with spondylitis predominating)		
Stage 1 Stage 2 Stage 3	0 2† 1†	3 5 10
Functional Class		
Class 1 Class 2 Class 3 Class 4	0 7 6 12	7 13 16 30

^{*} Duration of disease unknown in one of the positive and one of the negative cases. † These positive patients had combined disease.

TABLE 4

	Number of	Cases (58)
	Positive (25)	Negative (33)
Abnormal Physical Findings		
Rheumatoid nodules Significant lymphadenopathy	117	6
Splenomegaly	5	1
Abnormal Laboratory Findings		
Anemia	15	11
Leukopenia	4	1
Elevated sedimentation rate	23*	30
Positive STS	0 9 8	1
Elevated serum globulin	9	8
Decreased serum albumin	8 9†	10
Abnormal EKG	6	4
Abnormal urinalysis	0	4
Treatment with Drugs Possibly Associated with a Positive Lupus Phenomenon		
ACTH or steroids	6	10
Phenylbutazone	1	1
Hydralazine	0	0
Penicillin reactions	0.	0
Chrysotherapy at Any Time	0	3

* Not available in one case.

† Not available in three cases.

groups had been ill for 10 or more years and were over the age of 50. This preponderance of an older age group is due primarily to the deliberate selection of patients with far advanced disease.

The patients were classified according to type, stage and functional class of disease. Those designated as "peripheral" had evidence of involvement of extremities alone, with no significant history or roentgenologic findings of rheumatoid spondylitis. Those considered to be "spondylitis" had clinical and x-ray involvement of sacro-iliac joints and spine. If the hips or shoulders were also involved, the patient was still considered to be a "pure" spondylitic, but if there was any significant degree of rheumatoid arthritis in other peripheral joints the patient was designated as having "combined" disease. On this basis there were 18 positive cases of "peripheral" disease and seven of the "combined" form. Not one pure spondylitic demonstrated a positive L. E. test, although 11 such patients were studied.

The stage of disease had to be classified into two separate catagories. All patients who had peripheral disease or combined disease, which was predominantly peripheral, were classified in the four stages of increasing severity according to Steinbrocker et al.⁴¹ As can be seen from table 3, there was a predominance of positive patients with the advanced disability of stages 3 and 4. All patients with pure spondylitis, or with combined disease in which the picture of spondylitis was predominant, were classified in three stages according to Smyth et al.,⁴² and their incidence is also indicated in

table 3. It should be emphasized that the three positive cases in this group all had combined disease. Finally, all patients were classified functionally according to Steinbrocker et al. 41 It will be noted in table 3 that the majority were significantly disabled.

For this study we have considered Felty's syndrome to be rheumatoid arthritis having the additional findings of splenomegaly, leukopenia, and anemia with a hyperplastic bone marrow. Five of the patients (four positive, one negative) fulfilled these criteria. Three were women and two were At the time of study their ages ranged from 41 to 61 years, and the duration of the disease ranged from 13 to 23 years. All displayed the peripheral type of disease in stage 4 and functional class 3 or 4. Rheumatoid nodules were observed in all five patients. Three of them (two positive, one negative) underwent splenectomy, with clinical and hematologic improvement in two. The third patient (case 1) subsequently died of a severe infection. The high incidence of Felty's syndrome in this series is due to partial selection of cases from an anemia clinic to which they had been referred because of hematologic manifestations.

In general, there were no significant differences in the clinical histories of the positive and the negative groups. Therapy within a period of six months prior to the performance of the L. E. test did not play an important rôle in the production of the L. E. phenomenon. Of the 25 positive patients, only six gave a history of significant recent therapy with cortisone. One additional case had received a two-week course of phenylbutazone three months prior to the performance of the test. A subsequent L. E. test one year later was still strongly positive. None was given hydralazine, and

none reported a serum sickness-like reaction to penicillin.

The physical and laboratory findings in the positive group were compared with 33 negative patients (table 4). The groups roughly parallel each other with two exceptions: there was a greater incidence of rheumatoid nodules (11 of 17) and of Felty's syndrome (four of five) in the positive

In a search for possible features of systemic lupus erythematosus, a specific survey of the positive patients was made. None demonstrated a patchy alopecia or the classic dermatologic lesions of systemic lupus erythematosus. No patient demonstrated a positive serologic test for syphilis, and there was no evidence of acquired hemolytic anemia or circulating anticoagulants. Pleural effusions were observed on two occasions. In one patient (case 3) this was attributed to an infectious process, and in the other it was associated with congestive heart failure. Nine patients had abnormal electrocardiograms, six being associated with hypertension or evidence of coronary arteriosclerosis. Of the remaining three, two had an unexplained first degree heart block and the other (case 1) a pericarditis. Six patients presented abnormal urines; five of these were associated with chronic pyelonephritis or hypertension, but the cause of one could not be determined.

SHEEP CELL AGGLUTINATION TESTS

The sera of 23 of the 25 positive patients were tested with the sheep cell agglutination test using the euglobulin fraction (Ziff et al.⁴³). Positive reactions with a titer of 1:28 or above were obtained in 18 patients, and five were negative. Of the latter, two had combined disease with severe spondylitis. Ziff ⁴³ reports that approximately 90% of all cases of rheumatoid arthritis demonstrate a positive reaction, but found that patients with spondylitis or psoriasis are usually negative. For comparison, a group of 15 patients with systemic lupus erythematosus was also studied. Of these, six had negative and nine had positive reactions. In the latter group, seven had definite arthritic changes suggestive of rheumatoid arthritis, while none of the negative patients displayed these findings.

This phase of the study is now under further investigation and will be

reported separately at a future date.44

CASE REPORTS

The following case histories of five patients exhibiting the L. E. phenomenon are representative of the group studied.

Case 1. A 61 year old white man was hospitalized in April, 1955, because of an exacerbation of arthritis in association with fever and recurrent respiratory infections. He had first noted transient arthralgia of the hands, wrists and feet at age 39. Five years later he developed painful, swollen elbows. Subsequently there was a severe and progressive deforming arthritis. Treatment consisted of rest, salicylates

and physiotherapy.

Physical examination revealed an emaciated, chronically ill individual with evidence of far advanced but relatively inactive rheumatoid arthritis (figures 3A, 3B). The spleen was palpable. A significant anemia and a leukopenia as low as 1,400 white blood cells were present. A differential count revealed as many as 64% lymphocytes. The marrow was hypercellular. An electrocardiogram revealed low voltage, and the L. E. preparations were markedly positive. The sheep cell agglutination test was positive in a titer of 1:896. The patient was considered to fulfill the criteria for Felty's syndrome, and splenectomy was performed. Histologic review of the spleen failed to reveal evidence for systemic lupus erythematosus (figure 4A). Postoperatively the leukopenia was corrected. The patient gained weight and his appetite improved.

Three months after discharge the patient was rehospitalized with clinical and radiologic evidence of hypostatic bronchopneumonia. He responded poorly to therapy

and died.

Postmortem examination revealed: (1) bronchopneumonia; (2) obliterative pericarditis, and (3) minimal nephrosclerosis (figure 4B). No evidence of systemic lupus erythematosus was found.

Comment: The patient's clinical appearance and course after splenectomy satisfied the criteria for Felty's syndrome. He had had far advanced but relatively inactive rheumatoid arthritis of the peripheral joints for 22 years.

Case 2. A 62 year old white female has been permanently hospitalized since September, 1951, because of incapacitating joint deformities. She first developed

painful swelling of the right wrist and both knees at the age of 17. There was gradual progression of the disease, with additional involvement of the hips, feet and elbows, until she became bedridden 22 years later at the age of 48. Nine years later she developed psoriasis.



Fig. 3. A. (above) Photograph of hands (case 1), showing typical changes of rheumatoid arthritis. B. (below) X-rays of hands (case 1).

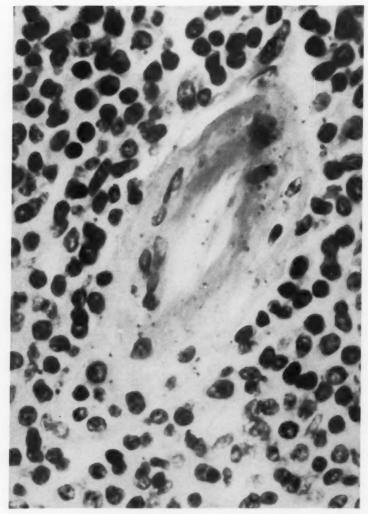


Fig. 4. A. Spleen (high dry), case 1. Note the smudgy appearance of the wall of the small arteries.

At the present time she has far advanced deformities of the hands (figures 5A, 5B) and feet, with flexion contractures of the knees and complete ankylosis of the hips in flexion. There is complete obliteration of the sacro-iliac joints radiologically.

Three months prior to the demonstration of a positive L. E. preparation, the patient received phenylbutazone, 300 mg, daily, for a period of two weeks. One year later the L. E. test was still strongly positive. The sheep cell agglutination test has ranged from 1:56 to 1:224 in titer.

Comment: This is a patient with severe, relatively inactive rheumatoid arthritis of the combined form. Although her L. E. tests remain strongly positive, she has been under observation for five years and reveals no clinical evidence of systemic lupus erythematosus.

Case 3. A 62 year old white man has been permanently hospitalized since May, 1945, for incapacitating arthritis. He first experienced painful swollen ankles at the age of 45. Three years later he developed generalized psoriasis and bilateral corneal ulcerations. His arthritis progressed rapidly, with deformities, subluxation and ankylosis, so that he became bedridden within the next two years. He subsequently developed involvement of the spine which progressed to complete ankylosis. His

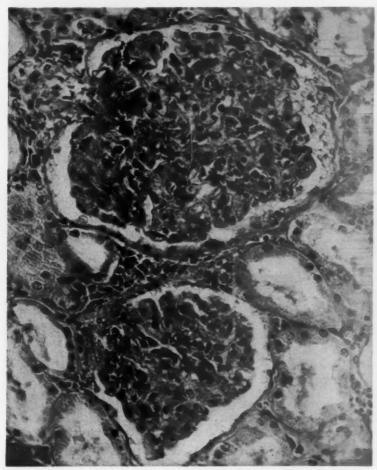


Fig. 4. B. Kidney (high dry), case 1. Focal indistinct thickening of the basement membrane with increased cellularity.



fingers began to "buckle," so that at the present time he has a typical "opera glass"

hand (figure 6A).

One year ago the patient developed an episode of fever, pain in the chest, cough and dyspnea. X-rays showed a loculated pleural effusion. Fluid obtained by thora-

centesis revealed no unusual laboratory findings. He was treated with penicillin

and made a rapid and complete recovery.

Laboratory study revealed a persistent albuminuria, with occasional cellular elements and granular casts in the urinary sediment. A renal biopsy revealed mod-

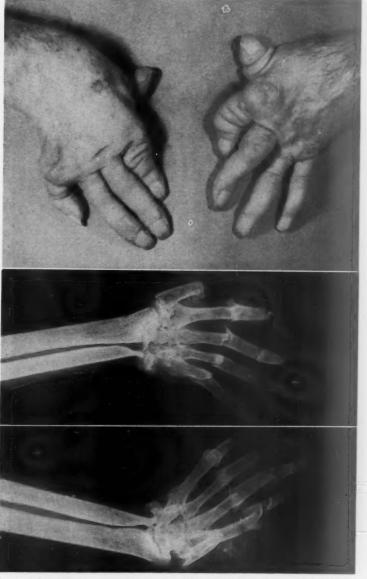


Fig. 6. A. (above) Photograph of hands (case 3). B. (below) X-rays of hands (case 3).



Fig. 7. A. (above) Photograph of elbows, forearms with nodules, hands (case 4).
B. (below) X-rays of hands (case 4).

erate renal arteriosclerosis and arteriolar nephrosclerosis.* X-rays indicated far advanced changes of rheumatoid arthritis in association with marked bone resorption (figure 6B). The L. E. preparation was positive on several occasions. The sheep cell agglutination test gave a titer of 1:28.

Comment: This is a patient with very severe rheumatoid arthritis involving both the peripheral joints and the spine. Clinical activity at this time is minimal. The pleural effusion in the last year was thought to be due to an infection and not to be a manifestation of systemic lupus erythematosus.

Case 4. A 44 year old white female was hospitalized in June, 1954, because of anemia and arthritis. Her illness had begun at the age of 21 with acute painful swelling of the fingers of the left hand, and then had recurred periodically, with involvement of the hands, knees and feet, producing crippling deformities with difficulty in walking.

Physical examination revealed the changes typical of far advanced rheumatoid arthritis of the hands, feet and knees, with flexion deformities of the digits, ulnar deviation, subluxation and ankylosis. Rheumatoid nodules were seen over both elbows and along the ulnar region of the forearms (figure 7A). The spleen and

liver were palpable.

The laboratory tests revealed an anemia and a leukopenia. The blood film, marrow, gastric analysis and Schilling test were compatible with the diagnosis of pernicious anemia. X-rays of the hands and feet revealed periarticular osteoporosis, narrowing of the joint spaces, marginal erosions and subluxations, all characteristic of rheumatoid arthritis (figure 7B).

The patient's anemia was corrected by vitamin B₁₂ therapy. However, the leukopenia persisted and the patient's rheumatoid arthritis remained active, with some

joint inflammation and pain.

A diagnosis of Felty's syndrome was then made and splenectomy was performed. Histologic study of the spleen revealed no evidence of lupus erythematosus. Following surgery there was an excellent clinical response, with a marked improvement in joint pain and a general feeling of well being. The patient was able to walk without the aid of crutches for the first time in many years. The leukopenia was corrected, and the subcutaneous nodules regressed considerably. L. E. preparations have remained positive. The sheep cell agglutination test was positive in a titer of 1:3584.

Comment: The patient presented severe, longstanding rheumatoid arthritis with Felty's syndrome and pernicious anemia. The rheumatoid arthritis and the leukopenia improved only after splenectomy. The patient is now doing well and has no clinical evidence of systemic lupus erythematosus.

Case 5. A 40 year old white male was hospitalized in May, 1955, because of arthritis. He had first developed stiffness and pain in the low back region at the age of 29. A diagnosis of rheumatoid spondylitis was made, and deep x-ray therapy resulted in considerable improvement. The next year he was hospitalized with a classic episode of acute glomerulonephritis, from which he recovered. Repeated clinical and laboratory evaluations since then have revealed no evidence of renal disease.

*We are grateful to Dr. Robert M. Kark and Dr. Victor Pollak for the performance and interpretation of the renal biopsy.

By the present admission he had lost 5 inches in height. There was complete rigidity of the entire spine, with flexion contractures of the hips and left knee (figure 8A). There were swelling and thickening of the periarticular structures of the wrists, elbows and knees, with acute inflammation of the ankles. X-rays of the spine revealed complete obliteration of the sacro-iliac joints and extensive paravertebral calcification (figure 8B).

Renal function tests were normal. The L. E. preparation was positive. Sheep cell agglutination tests were negative. The patient had received no steroid therapy except for injections of hydrocortisone into the left hip joint two years previously.



A B Fig. 8. A. Profile of case 5. B. X-ray of spine (case 5).

Comment: This is a patient with typical rheumatoid arthritis of the spine, with additional involvement of some peripheral joints, an example of "combined disease" (primarily spinal). The episode of renal disease at the age of 30 left no residual damage and was thought to be typical of acute glomerulonephritis and not of systemic lupus erythematosus.

ELECTROPHORETIC ANALYSIS OF SERUM PROTEINS

Serums from 51 patients were fractionated by paper electrophoresis. Twenty-four of these patients exhibited the L. E. phenomenon.

Electrophoretic analysis was performed at pH 8.6 on apparatus similar to that described by Osserman and Lawlor. The following values were obtained by dye elution in 21 normal adult subjects: gamma globulin,

* Because of errors inherent in dye elution, 46 our values are not comparable to those determined by other methods.

 1.89 ± 0.19 ; beta globulin, 1.25 ± 0.21 ; alpha 2 globulin, 0.86 ± 0.15 ; alpha 1 globulin, 0.41 ± 0.09 ; and albumin, 3.24 ± 0.28 . Values exceeding 2.09 S.D. were considered abnormal, with 95% confidence limit.

The 51 patients were divided into positive and negative groups for com-

parison of protein changes (table 5).

The greater frequency of gamma globulin elevations in the positive group conforms to the usual finding in systemic lupus erythematosus, 47, 48 in which gamma globulin increases are the rule. However, one cannot predict a positive reactor on the basis of a high gamma globulin alone, for several patients in the negative group also presented a substantial increase. There

 ${\bf TABLE~5}$ Serum Protein Alterations in Rheumatoid Arthritis

	Group I (24 Patients) (Pos. L. E. Prep.)	Group II* (27 Patients) (Neg. L. E. Prep.)	Total 51
Normal Pattern	2	5	7
Gamma Globulin			
Elevation	10	4	14
Depression	4	2	6
Beta Globulin			
Elevation	0	1	1
Depression	2	4	6
Alpha 2 Globulin			
Elevation	3	3	6
Depression	0	1	1
Alpha 1 Globulin			
Elevation	0	2	2
Depression	1	1	2
Albumin			
Elevation	0	0	0
Depression	17	16	33

^{*} Eight of these were spondylitics.

was no single protein alteration or characteristic pattern for either group. The high incidence of low albumin in both groups is a common finding in chronic rheumatoid arthritis. 49, 50, 51, 52, 58

Eight patients, all in the negative group, presented rheumatoid spondylitis without peripheral articular involvement. One presented a normal electrophoretic pattern, while five gave low values for albumin. Globulin changes were inconspicuous except for the gamma fraction, which was depressed in three and mildly elevated in one.

The electrophoretic data demonstrate that the factor responsible for the L. E. phenomenon in these patients is not solely dependent upon quantitative changes in the serum proteins. On the other hand, positive reactors are more likely to show gamma globulin elevations.



Fig. 9. Lymph node (low power). Note the distinct lymphatic follicles with large germinatal centers.



Fig. 10. Rheumatoid nodule (low power). Fibrinoid necrosis with some palisading of the mesenchymal cells, chiefly fibroblasts, around the necrotic zone.

SURGICAL PATHOLOGIC LESIONS

Lymph Nodes (figure 9): The lymph nodes from four patients with positive L. E. preparations were studied and compared with lymph nodes from two patients with negative preparations, as well as those from patients with known systemic lupus erythematosus. In all groups the nodes were characterized by enlargement, thickening of the capsules, distortion of the normal architecture, diffuse proliferation of lymphoid and reticulum cells, follicular hyperplasia, and focal areas of fibrosis, with a tendency to palisade formation and slight thickening of the walls of the arteries and sinusoids. In every instance the pathologic impression was that of severe lymphadenitis.

Rheumatoid Nodules (figure 10): Nodules located about the elbow were obtained from two patients with positive and two with negative preparations. The characteristic picture of a rheumatoid nodule consisted of a central zone of eosinophilic necrotic material (fibrinoid degeneration and necrosis), surrounded by a zone of palisading fibroblasts.

Spleen: Splenectomy was performed on three patients with Felty's syndrome. Two (cases 1 and 4) had positive L. E. preparations and one had a negative preparation. The histology of the spleen in all three cases revealed primarily capsular thickening, normal or somewhat enlarged follicles with reticulum cell proliferation, smudginess of the wall of the central arteriole (figure 4a), and dilatation and glandlike appearance of the sinusoids due to swelling of the lining endothelial cells. Some fibrosis and marked congestion were seen in each instance.

Comment: The pathologic data did not reveal the specific lesions of systemic lupus erythematosus in any case. No significant differences appeared between the negative and the positive groups. The changes observed in the lymph nodes have been described in both systemic lupus erythematosus and rheumatoid arthritis, 54 and have often been confused with lymphoma.

DISCUSSION

The incidence of positive L. E. preparations reported in this series is greater than in any previous study. A number of factors may have contributed to this high incidence. First, all slides were studied by two qualified observers using a standardized, controlled reading procedure. Second, the most sensitive technics available were used. Third, since nucleophagocytosis and tart cell formation occur frequently in positive preparations, all cases presenting only this phenomenon upon initial examination were restudied. The latter resulted in the disclosure of eight additional positive cases.

The type of patient studied may be important. The majority presented far advanced, long-standing rheumatoid arthritis, and many had been permanently institutionalized. Also, therapy was not a factor in the production of the L. E. phenomenon, since only one patient was receiving large amounts

of cortisone, and only five others had received cortisone within six months of the study.

The only distinguishing features observed in the positive group included the absence of patients with "pure" spondylitis, and a high incidence of rheumatoid nodules and of Felty's syndrome, as well as a greater frequency of elevated gamma globulin as determined by serum electrophoresis. Otherwise, in terms of age and sex composition, historical data, abnormal physical and laboratory findings and response to therapy, the two groups were essentially alike.

If one compares the clinical features of systemic lupus erythematosus as described in recent years with the classic descriptions of rheumatoid arthritis, a wide overlapping of clinical and laboratory findings will be observed. It is not surprising, therefore, that the findings elicited in both the positive and the negative groups in this study have also been described as occurring in systemic lupus erythematosus. Features characteristic of this disease, however, did not appear in the present study. Pathologic lesions considered diagnostic of systemic lupus erythematosus, such as hematoxylinophilic bodies, the wire-loop lesion of the renal glomerulus, and the onion peel thickening of the arteries were not demonstrated. The sheep cell agglutination test failed to differentiate the patients with rheumatoid arthritis and positive L. E. tests from those with known systemic lupus erythematosus. Finally, the prognosis of untreated systemic lupus erythematosus is poor, yet the average duration of illness in the positive group, most of whom had never received steroid therapy, was 19 years.

On a theoretic basis, one might postulate the existence of a spectrum of diseases of common etiology, with chronic rheumatoid arthritis at one end and severe classic systemic lupus erythematosus at the other. At the point where these entities overlap the manifestations of both might coexist in varying degrees. The clinical picture presented would then depend upon

the chronicity, severity and nature of the target organs involved.

In conclusion, the evidence presented in this study indicates that the L. E. phenomenon may occur in patients with rheumatoid arthritis as a nonspecific reaction of unknown etiology. The diagnosis of systemic lupus erythematosus should not be made in patients with rheumatoid arthritis who have a positive L. E. test unless it can be confirmed by other evidence. Above all, the prognosis and choice of therapy in such patients should not be based upon the results of a single laboratory examination.

SUMMARY

1. The L. E. phenomenon was found in 25 of 91 patients presenting the classic clinical picture of rheumatoid arthritis. Therapy did not influence the incidence of positive preparations in this study.

2. Rheumatoid nodules, Felty's syndrome and an elevated electrophoretic gamma globulin occurred more frequently in the group with the positive

L. E. preparations. None of these patients presented pure rheumatoid spondylitis. The patients with the positive preparations were otherwise similar to the patients with negative preparations.

3. Pathognomonic features of systemic lupus erythematosus were not

observed in any patient.

4. It is concluded that the L. E. phenomenon may occur in patients with rheumatoid arthritis as a nonspecific reaction. The diagnosis of systemic lupus erythematosus in such patients, therefore, should be based upon other criteria.

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SUMMARIO IN INTERLINGUA

Novanta-un patientes con arthritis rheumatoide esseva evalutate in re le presentia del phenomeno de lupus erythematose (L.E.). Le evalutation esseva effectuate ab le puncto de vista clinic e per methodos laboratorial, incluse studios histologic de nodulos subcutanee, de nodos lymphatic, e del splen. Le preparatos a lupus de iste gruppo de patientes e de un gruppo de 50 subjectos de controlo esseva studiate como entitates non-identificate per duo del autores. Typic cellulas de L.E. esseva constatate in 25 del 91 patientes sed in nulle del subjectos de controlo.

Le majoritate del patientes habeva sever grados de chronic arthritis rheumatoide. Le gruppo con positive preparatos a lupus includeva 18 patientes con arthritis rheumatoide peripheric, durante que septe habeva combinate affectiones peripheric e spinal. Spondylitis "pur" non esseva representate. Dece-un del patientes L.E.-positive habeva typic nodulos rheumatoide. Quatro casos presentava le syndrome de Felty. In tres de istos, splenectomia esseva effectuate, e studios histologic non revelava alterationes specific pro lupus erythematose. In un del tres, le subsequente necropsia contribueva nulle substantiation de lupus. Sex del 25 patientes con cellulas de L.E. habeva recipite un curso de cortisona e un habeva recipite phenylbutazona intra le sex menses precedente le studio.

Le gruppo positive exhibiva un augmentate incidentia de nodulos rheumatoide e del syndrome de Felty e etiam un elevation de globulina gamma (manifeste per tests electrophoretic), sed alteremente le gruppo resimilava le gruppo negative in omne respectos. Es formulate le conclusion que un positive phenomeno de L.E. pote occurrer in un significative numero de patientes con arthritis rheumatoide sin necessarimente indicar le presentia subjacente de disseminate lupus erythematose.

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OBSERVATIONS IN THE MANAGEMENT OF LATE ARTERIOSCLEROSIS OBLITERANS WITH GANGRENE*

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One rarely has the opportunity to observe the panorama of a single ailment unfold itself over a broad span of years. It has been my privilege to follow, at first hand, the clinical picture of arteriosclerosis obliterans associated with gangrene and/or ulceration of the extremities for the years following World War II, 1946 through 1956. During that decade 1,158 patients, 643 males and 515 females, were hospitalized at the Queens General Hospital with varying degrees of gangrene of the extremities associated with arteriosclerosis obliterans. Seventy-nine per cent of these people were over 60 years of age.

Observations of these patients in the hospital were supplemented by a very efficient home care service plan and also by follow-up studies at the Peripheral Vascular Disease Clinic, an out-patient department service which provided for care of ambulatory patients as well as an in-patient consultation service. As a result of the combination of these three agencies, it was possible to integrate our management so that some of these patients were observed continuously for a period of as long as six years. Of the 1,158 patients under consideration, 303 died, and 589 underwent amputation, the greater percentage of which were major amputations above the knee. Of these latter 443 survived amputation and 146 died postoperatively, accounting for almost half of the total 303 mortalities.

From these high mortality and morbidity figures we may deduce that this was an extremely deteriorated group of patients. There was a high incidence of associated cerebrovascular disease, hypertension, diabetes mellitus, cardiac decompensation with associated cardiac arrhythmias, mental aberrations and many other systemic diseases.

Such an analysis projects management along two lines: first, the consideration of the systemic disease and its effects upon the circulation of the extremities; second, the limiting effect of extensive systemic disease upon the vigor of therapy calculated to improve peripheral blood flow into the extremities.

Although no specific method has been established to prevent the development of arteriosclerosis obliterans, there are certain traumatizing agencies, chemical, thermal and mechanical, which precipitate gangrene. In a large

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number of instances these injuries are avoidable. Minor breaches of good foot hygiene frequently precipitated injury or infection which resulted in gangrene. Inadequate indoctrination in good foot care, aggravated by indifference, mental incapacity or an unfounded dependence upon some more dramatic form of therapy, was a factor in these hygienic breaches.

Early active treatment calculated to overcome infections prevented gangrene more consistently than any other form of therapy. The use of appropriate systemic antibiotics, associated with bland local therapy, has time and again overcome infection which in the pre-penicillin era would have developed into local thrombosis and gangrene. The period of therapy must be prolonged and the dosage large. No doubt effective antibiotic therapy has converted many a potential gangrene into a viable extremity.

According to Barker, Hines and Kvale, anticoagulants provide a means of preventing extending thrombosis. They may produce a more favorable medium in the intravascular clot for the action of natural enzymatic anticoagulants to recanalize thrombosed vessels. Wessler and Silberg have shown, by their careful anatomic studies of the pathology of the small vessels in the leg associated with gangrene, that fresh thrombosis was consistently associated with necrosis in the distal portions of the extremity. The presence of extending thrombosis so obstructed the anastomotic interarterial pathways that vessels already obstructed by recurrent thrombi could not utilize this collateral circulation. If propagation of this fresh thrombus could be prevented by the use of anticoagulants, continuity of blood flow could be maintained in spite of patchy thrombotic occlusion of arterial segments.

Postoperative or postcoronary shock, with a resulting reduction of blood flow to the extremities, has precipitated thrombosis and gangrene. Can anticoagulants prevent thrombosis in the presence of shock? Unfortunately, patients with arteriosclerosis obliterans present many relative contraindications to the use of anticoagulants. Such therapy must be prolonged and very carefully controlled. These elderly people do not lend themselves to prolonged hospitalizations or rigorous restriction.

In our own series, heparin and Dicumarol were used in eight patients during the acute phase following thrombosis prior to the onset of actual necrosis of tissue. It is too early to tell whether the results observed in this small number of people warrant the use of this therapy. The results are definitely encouraging. The theoretic indications for the use of anticoagulants in arteriosclerosis obliterans, where preformed collateral channels remain relatively patent and available for immediate use by the open segments of the major leg arteries, seem to be on as solid a foundation as is the use of anticoagulants in the therapy of coronary artery disease.

In our preoccupation with the circulation of the extremities, we tend to neglect the factors which regulate systemic blood flow. A cardinal consideration is the condition of the heart in relation to circulation. Cardiac arrhythmias, cardiac decompensation and operative procedures, all having as their common denominator a fall in blood flow to the extremities, often preceded and may have precipitated gangrene. The feeding of small emboli into the extremities by a fibrillating heart or a mural thrombus associated with a myocardial infarction or fragments from an aortic intima disrupted by atheromatous damage may not necessarily manifest themselves as an acute embolic phenomenon of classic description, but rather as a more gradually developing thrombotic process seeded by these small emboli. Consequently the use of digitalis, quinidine, blood transfusions, norepinephrine, diuretics, anticoagulants or any other procedures calculated to improve systemic blood flow and the quality of systemic blood and reduce hypotensive effects in the extremities can frequently serve more effectively to improve peripheral blood flow than can the various vasodilator drugs used nominally and specifically for that purpose.

The vast majority of patients hospitalized for arteriosclerosis obliterans had such extensive systemic pathology that the former condition was only a part—frequently a lesser one—in the total picture of this disease. One attempts to conserve as much tissue as possible by performing minor amputations where gangrene exists. Removal of individual toes or several toes, transmetatarsal amputations or even midleg amputations succeeded only when the underlying circulation was adequate to heal the surgical wound.

When sufficient time had elapsed between the onset of gangrene and the performance of a minor amputation, this fact would be indicated by a clear demarcation of the necrotic tissue and pink, warm, healthy skin adjacent to Under these conditions the gangrenous tissue could be debrided distal to the zone of junction, and the small amount of residual necrotic tissue permitted to slough spontaneously. If this state of the necrotic area cannot be achieved, minor amputation almost invariably fails. The better the underlying circulation, the more rapid the development of demarcation in the acral parts. Local enzymatic therapy with preparations of streptokinase and streptodornase and the trypsin enzymes may provide a method of debridement in necrotic tissue.⁵ Surgical local debridement might penetrate the protective junctional zone between normal and gangrenous tissue, opening the way for the spread of infection. A form of superficial local selective debridement which would leave viable tissue intact but remove necrotic tissue and coagulated occluding discharges could provide an avenue of escape for the purulent secretions which tend to collect and obstruct drainage. Injurious compression of local tissue and focal growth and spread of pathogenic bacteria could be avoided. Our experience with enzymatic local debridement used in the presence of tissue devitalized by grossly inadequate circulation has been mixed.

It is probable that injured tissue which might be potentially viable is attacked and destroyed by these enzymes. Severe burning was experienced at the site of application in three out of 18 patients treated. However, on

three infected necrotic amputation stumps, where necrosis existed adjacent to adequate circulation, enzymes acted very effectively in clearing up slough. Enzymatic debridement is expensive. The action of the enzymes is superficial and brief in duration, and their application frequently presents practical difficulties. We are not convinced that their use is more advantageous than simple intermittent saline or mild antiseptic soaks in clearing away debris.

Midleg amputations frequently succeeded even in the absence of a palpable popliteal or femoral pulse, but it was found that unless the patient was cooperative and the circulation reasonably good, contractures developed in the knee joint which prevented the utilization of an artificial limb and created a clumsy, redundant, useless stump which healed very slowly and developed

pressure sores and local irritation.

The knee joint should be preserved if possible. The midleg amputation is less shocking than the supracondylar or low thigh, but in the aged patient it is unusual to obtain a functioning knee joint and a healed stump in an individual who has sufficient systemic cardiac capacity to utilize an artificial limb. The level of amputation is an individual problem, governed primarily by the condition of the local circulation and the general condition. The status of the other extremity, the mentality and morale of the patient, and his desire to free himself from a bed or wheelchair existence play a large part in the ultimate utilization of a prosthesis.

In not one single case where gangrene existed and it was deemed necessary or advisable to perform a major amputation for this reason did sympathectomy, intraarterial Priscoline injections, lumbar paravertebral blocking, the use of trypsin enzyme either locally or systemically, the systemic use of vasodilator drugs or various forms of physiotherapy obviate the necessity for amputation or convert a major into a minor amputation.

Sympathectomies (of which 157 were done in this series), intra-arterial injections of Priscoline and lumbar paravertebral blocking, all methods of removing the vasoconstrictor tone of the sympathetic nervous system in a single extremity, did speed healing of superficial ulceration. When trophic changes were already present in the fingers or toes, vasodilating measures did not help. There were several instances where digits with marginal circulation became frankly gangrenous after sympathetic release. In some instances a painful extremity became more painful after a vasodilating procedure. Chemical sympathectomy produced by systemic vasodilators sometimes caused disturbing postural hypotension, and frequently added to the patient's woes by creating digestive disturbances. There were no known instances of myocardial infarction produced by chemical vasodilators in this series. The end result of the general vasodilating effect was to reduce blood flow to the diseased extremity.

Obstruction in arteriosclerosis obliterans begins in the major arteries of the leg from knee to ankle.³ The posterior tibial artery and its branches become involved first in a segmental type of thrombosis. The anterior tibial

and its branches are subsequently similarly obstructed. Minor amputations fail under these circumstances because a circulation inadequate to sustain viability in an acral part can hardly be expected to support healing after a surgical operation. Arterial grafting calculated to bypass segmental obstructions in the femoral artery usually fails to save an extremity in an aged deteriorated patient because the small distributing vessels in the leg are obstructed. Rarely, a femoral arterial segment may be occluded with leg arteries sufficiently patent to serve as adequate distributing vessels. These conditions are seen in patients with a minimal previous clinical history of occlusive arterial disease, and are unlikely to be associated with gangrene, but rather manifest themselves as intermittent claudication. Such a state of the circulation may be demonstrated by arteriography.⁴ In such instances arterial grafting may prove highly successful provided the graft remains patent.

Patients in very toxic states resulting from absorption from an infected and gangrenous extremity can be maintained in refrigeration by packing the extremity in finely ground ice until toxicity can be overcome. Refrigeration provides, in effect, a "physiologic amputation." Permission to amputate must be obtained before refrigeration is started. Refrigeration will not save

a limb but may save a life.

In summary, the best way to prevent gangrene is to protect the patient from trauma—physical, chemical or thermal—and to overcome local infection by early and active antibiotic therapy. Efficient management of anemia, cardiac arrhythmias and cardiac decompensation, and the prevention, if possible, of sharp declines in blood pressure, with resulting fall in peripheral blood flow, are simple, useful, practical therapeutic procedures. To determine the level of amputation, one must evaluate the individual merits of each patient, keeping in mind his mental as well as physical status.

Once gangrene has developed, spread of infection can be combatted by providing adequate drainage for exudates retained at the zone of junction between viable and gangrenous tissue. Minor amputation should be post-poned until clear demarcation has been established. Such amputations should be in the nature of debridements distal to the zone of junction. Lumbar sympathetic nerve surgery, prompted by desperation in the presence of gangrene, failed consistently to prevent amputation or to reduce the extent of amputation.

SUMMARIO IN INTERLINGUA

Inter 1946 e 1956, 1.158 patientes esseva observate al Hospital General Queens de Jamaica, New York. Omnes habeva avantiate arteriosclerosis oblitterante con gangrena o con ulceration del extremitates. Esseva trovate que le melior maniera de prevenir gangrena in le presentia de un marcatemente reducite circulation es proteger le extremitate contra trauma. Si cellulitis o un ruptura cutanee occurre, un adequate tractamento antibiotic active es indicate. Si gangrena superveni, le uso de un therapia de vasodilatation generalisate es de valor questionabile. Le curation

de ulcerationes superficial pote esser accelerate per sympathectomia lumbar, Priscolina intra-arterial, e bloco de nervo sympathic lumbar. Enzymas trypsinic—in applicationes local o in applicationes systemic—es de pauc valor. In certe casos illos es mesmo nocive. Post que gangrena se ha disveloppate de maniera que amputation es indicate, il non es possibile prevenir le amputation o reducer su magnitude per le effectuation de sympathectomia. Sub certe conditiones illo pote mesmo precipitar le declaration de gangrena in un digito in stato marginalmente pre-gangrenose.

Therapia a anticoagulantes esseva probate in un parve numero de patientes. Il pare que iste tractamento es indicate pro prevenir le extension de thromboses con lor consequente reduction in le fluxo collateral. Amputationes minor debe esser effectuate post que le tessuto se ha demarcate. Le sito del amputation es alora le zona distal al junction de tessuto normal e gangrenose. Si demarcation non se disveloppa con un area normal adjacente al area necrotic, amputationes minor non debe esser

riscate.

Amputationes major, a nivellos sufficientemente alte pro assecurar le curation del vulnere chirurgic, non pote esser evitate si le dolores, le toxicitate, e le extension del processo necrotic non es subjicibile per un adequate tractamento medical.

Graffos arterial pote esser utilissime in casos de occlusion segmental in vasos major, specialmente in le region del bifurcation aortic e a vices in le arteria femoral (quando patentia del arterias distributive del gambas pote esser demonstrate

arteriographicamente).

Graffos arterial non succede si le arterias distributive in le gambas non es patente. Sub iste conditiones nulle therapia specific es disponibile a iste tempore. Le tractamento conservative—le mantenentia del plus efficace balancia inter vasodilatation e requirimentos metabolic e un militante attacco antibiotic contra le infection—remane le plus efficace mesuras contra gangrena.

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CLINICAL-PATHOLOGICAL CONFERENCE

HYPOPITUITARISM: CLINICAL-PATHOLOGICAL CONFER-ENCE AT THE NATIONAL INSTITUTES OF HEALTH*

Dr. Bunim: The case to be discussed this afternoon presented a difficult problem in management which obviously was not resolved. The patient was admitted with a diagnosis of adrenal insufficiency and developed an unexpected and uncommon terminal complication. Dr. Daniel Federman will present the case.

Dr. Federman: This was the first admission to the Clinical Center of a 52 year old white woman who entered with the chief complaint of weakness of seven months' duration. She was referred here because of failure to respond to what was considered adequate treatment for suspected adrenal insufficiency.

A right radical mastectomy had been done 20 months before admission. At surgery, an "inoperable" scirrhous carcinoma was found, and metastatic tissue was palpable beyond the reach of the dissection. The patient was treated with local radiation postoperatively. No detectable recurrence of the lesion at the site of surgery had developed.

Ten months before admission the patient developed polyuria, polydipsia, urinary frequency and nocturia, without dysuria, polyphagia or glycosuria. Her doctor made the diagnosis of diabetes insipidus and initiated treatment with pitressin tannate in oil. Her symptoms were well controlled by this therapy.

Between 10 and six months prior to admission the patient had three episodes of pneumonia consisting of cough, sputum, auscultatory changes, fever, and rather disproportionate prostration. The first two episodes were treated with penicillin, with apparent good response. During the third recurrence, however, hospitalization was necessitated by extreme weakness and an episode of prolonged syncope. A diagnosis of adrenal insufficiency was made and treatment with hydrocortisone was started. Because of pronounced fluid retention, prednisone was later substituted in doses of 30 mg. daily. At this time, pitressin powder inhalation was also prescribed.

Although initially she improved somewhat while receiving steroid replacement therapy, she soon noted increasing fatigue and weakness and was admitted to a different hospital. Here all steroid medication was discontinued, and the patient developed hypotension, tachycardia and fever, and became semicomatose. This reaction to discontinuance of steroid medication, plus previously demonstrated.

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strated failure to show a rise in urinary 17-ketosteroid excretion after the administration of ACTH intravenously, seemed to confirm the diagnosis of Addison's disease, and treatment with prednisone was resumed in daily doses of 30 mg.

She did not improve during the next four months, and was then referred to the Clinical Center. When admitted she was troubled by fatigability, weakness, intermittent generalized headache, increasing cold intolerance, numbness and paresthesias of distal portions of the extremities, puffiness of the eyelids, and blurring of vision in the lower half of the visual fields. In addition, she complained of severe burning in her throat on swallowing, progressive rounding of her face, and occasional difficulty in breathing.

Her history disclosed that a first and only pregnancy, at age 30, had terminated in a miscarriage at five months and was followed by severe bleeding and protracted anemia. At age 47, because of severe metromenorrhagia, a panhyste-

rectomy and oophorectomy were done. No malignancy was found.

On physical examination at admission the patient's temperature was 37° C.; pulse rate, 82/min.; blood pressure, 125/85 mm. Hg; respirations, 18/min. She lay in bed with her eyes closed, complaining of feeling weak and sick. She had a moon face and a pronounced "buffalo-hump." Her skin was dry but neither cool nor coarse. Her eyes were puffy, but her extraocular movements, visual fields and fundi oculi were normal.

The neck was supple; no thyroid tissue was felt. The right breast was absent and the mastectomy scar was well healed, but near the scar were numerous elevated, indurated purple nodules, 2 to 4 mm. in diameter, which gradually decreased in number during hospitalization. The patient stated that the nodules had persisted since radiation administered to the area. No lymph nodes were felt. The lungs were normal except for sticky inspiratory râles at the right base.

The heart was normal in size, rate, rhythm and sounds. Abdominal and pelvic examinations showed only absence of the uterus and adnexae. The extremities were normal.

Laboratory Data: Hemoglobin, 11.8 gm. %; white blood count, 8,200 cells per cubic millimeter; 82% neutrophils, 17% lymphocytes, 2 nucleated red cells per 200 white cells. Urinalysis: specific gravity, 1.021; pH, 7; sediment, negative. Total serum protein, 5.9 gm. %; albumin, 3 gm. %; blood urea nitrogen, 22 mg. %; serum calcium, 9.8 mg. %; phosphorus, 3.2 mg. %; serum alkaline phosphatase, 1.2 Bessey-Lowry units; sodium, 135 mEq./L.; chlorides, 105 mEq./L.; potassium, 4.2 mEq./L.

Roentgenographic studies revealed some bony demineralization of the skull and spine. There was no evidence of metastasis to the skull, lungs, spine, long bones or pelvis. The sella turcica was normal. X-ray films of the lungs showed

slight linear fibrosis in both bases.

Special examinations:

(a) The Carter-Robbins test was performed to determine the presence of diabetes insipidus. Pitressin was discontinued until the patient's polyuria recurred. She was then hydrated in order to obtain a constant urine flow, and hypertonic saline was given intravenously. Normal patients and patients with psychogenic polydipsia exhibit an antidiuretic response to this procedure, but persons with diabetes insipidus do not. No reduction in this patient's urine

output occurred. Following the test, pitressin, given intravenously, produced an immediate reduction in urine flow.

(b) The following tests of thyroid function confirmed the clinical impression of mild hypothyroidism: protein-bound iodine, 2.2 μ g. %; basal metabolic rate, minus 18%; radioactive iodine uptake, 23% in 24 hours, and serum cholesterol, 333 mg. %.

(c) In contrast to normal postmenopausal women, this patient excreted less than five mouse units of gonadotropins in her urine in a 24-hour period.

(d) Adrenal function was tested in two ways:

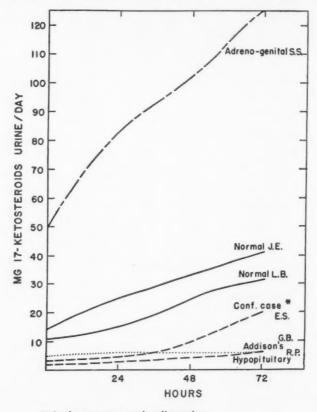
(1) After priming doses of ACTH were administered intramuscularly for three days, and while she was being given 1 mg. of delta-1-9 a-fluorohydrocortisone daily for replacement therapy, the patient was given ACTH intravenously for three days. Her plasma hydrocortisone and urinary corticoids, almost absent at the start of this study, rose promptly and rapidly to levels higher than are normally found in this test. Because of the discrepancy between these data and those of previous studies at another hospital which suggested the diagnosis of Addison's disease, further studies were undertaken.

(2) After priming doses of ACTH were administered intramuscularly again for three days, steroid medication was discontinued. Within two days of the last dose of ACTH the patient developed nausea, anorexia, increased weakness, and a diminution of awareness. These symptoms were followed by a tachycardia of 140 beats per minute, a drop in blood pressure to 76/58 mm. of Hg, and a fever of 38.5° C. Blood drawn at this time had a hematocrit of 37%, and the serum contained sodium 126 mEq./L. and potassium 3.3 mEq./L. There was no detectable level of plasma hydrocortisone. Saline solution given intravenously restored her blood pressure to 110/78 mm. Hg, and intravenous treatment with hydrocortisone and ACTH produced a prompt disappearance of the fever and other symptoms.

In an attempt thereafter to determine a satisfactory replacement dose of steroid, the patient was given up to 75 mg. of hydrocortisone per day. She also received tri-iodothyronine and pitressin intramuscularly, but did not improve. She remained weak and bedridden, complained of generalized headache, ate very little and vomited occasionally. Physical examination showed no significant changes other than a profound lethargy and a persistent tachycardia, slight ptosis of the right eyelid, and, on several occasions, a fever of 38 to 38.5° C. She was given infusions of 100 mg. of hydrocortisone on several occasions and felt notably better each time. She seemed to feel and look even better when she received ACTH.

Because of the persistent lethargy and headache a lumbar puncture was performed. The spinal fluid was clear and was under an initial pressure of 300 mm. of $\rm H_2O$. It contained 300 red blood cells, 200 white blood cells (50% neutrophils, 50% lymphocytes) per cubic millimeter, and a protein concentration of 365 mg. %. Cultures of the fluid grew abundant quantities of Torula. The patient continued in a poor condition and, for the first time, developed a stiff neck. A lumbar puncture was repeated and the initial pressure was 90 mm. $\rm H_2O$. A smear of an India ink preparation of the spinal fluid revealed Torula organisms.

Five days before death the patient gradually lapsed into coma and shock. No localizing neurologic signs could be found and, except for the change in mental state and vital signs, no difference from prior examinations was detected. Treatment thereafter included intravenous fluids, hydrocortisone, pitressin, penicillin, streptomycin, sulfadiazine, endomycin, noradrenalin and oxygen inhalation.



* Conference case under discussion

Fig. 1. Excretion of urinary 17-ketosteroids during continuous infusion of ACTH intravenously.

During the last two days there were physical and radiologic signs of consolidation in the right chest. The patient did not regain consciousness, but developed progressively rising fever, tachycardia, tachypnea and cyanosis. She died on the sixtieth hospital day.

Dr. Bunim: It is the policy of the National Institutes of Health to admit to the Clinical Center patients whose disease fulfills the requirements of a research project currently in progress.

The patient presented today was admitted because her endocrinologic disorder seemed to make her an excellent subject for the study of steroid metabolism in our investigations of the metabolism of hydrocortisone. Dr. Ralph Peterson will discuss some of the diagnostic problems this case presented.

DR. PETERSON: I shall present the results of our studies of the patient's adrenal cortical function. Our first step was to attempt to determine the level of her plasma hydrocortisone. Because we were unable to detect this corticosteroid in her plasma, we believed that she was suffering from one of three

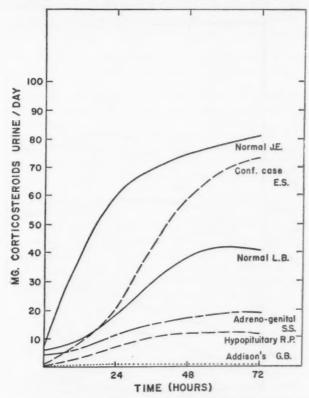


Fig. 2. Excretion of urinary corticosteroids during continuous infusion of ACTH intravenously.

possible disorders: Addison's disease, a state of suppressed adrenal cortical function due to prolonged use of prednisone and hydrocortisone, or hypofunction of the adrenal cortex secondary to some type of injury to the pituitary gland or to the hypothalamus. In order to differentiate between these possibilities, we determined excretion of steroids in the urine and the concentration of hydrocortisone in her plasma during a 72-hour period of continuous intravenous infusion of ACTH. Following this infusion, the administration of ACTH and exogenous steroids was discontinued abruptly and her clinical response noted. The results of her studies were compared with those of other patients with normal and abnormal adrenal cortical function.

Figure 1 shows the adrenal response, as measured by the urinary excretion of 17-ketosteroids, during the administration of ACTH. In the normal subjects (J. E., L. B.), there was a gradual rise in 17-ketosteroid output, and at 72 hours the amounts excreted in the urine were two to three levels of the control period. In a classic case of long-standing hypopituitarism (R. P.), there was only a minimal rise in urinary 17-ketosteroids at 72 hours from a baseline level that was below normal. In a case of Addison's disease (G. B.), no significant rise above

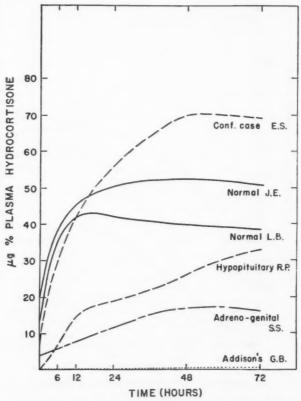


Fig. 3. Plasma hydrocortisone levels during continuous infusion of ACTH intravenously.

the low baseline level could be detected. The patient under discussion (E. S.) had a low baseline 17-ketosteroid output and showed a delayed, but significant, rise in the excretion of urinary 17-ketosteroids in 72 hours. A patient with the adrenogenital syndrome (S. S.) showed a prompt rise to very high levels from an abnormally high baseline level.

Figure 2 shows the changes in urinary excretion of corticosteroids during the same tests. The assay method employed measures about 20 to 30% of the total quantity of endogenously produced hydrocortisone each day.¹ In the

normal subjects (J. E., L. B.), whose baseline excretion levels were approximately 7 mg. per day, there was a prompt rise in corticosteroid output that reached a plateau on the second or third day. Although the magnitude of the response has been found to be quite variable in normal subjects, a five- to tenfold increase above the control level is consistently observed. In the patient with Addison's disease (G. B.), little or no corticosteroids appeared in the urine, and no detectable increase occurred after ACTH administration. In the patients with hypopituitarism (R. P.) and with the adrenogenital syndrome (S. S.), a very slow and inadequate rise in corticosteroid excretion above low baseline levels was noted.

The excretion of corticosteroids in the urine of patient E. S. was much below normal before ACTH was given, but during the infusion the values rose to levels in the normal range.

Figure 3 shows the changes in the concentration of plasma hydrocortisone during ACTH infusions. The results closely parallel data shown in figure 2. In the normal subjects (J. E., L. B.), the rise in plasma hydrocortisone occurred more promptly than the rise in urinary corticosteroid excretion and reached a plateau earlier. Plasma concentrations greater than 50 to 60 µg. % are seldom observed in a normal subject. The patient with Addison's disease (G. B.) exhibited very low or immeasurable concentrations of plasma hydrocortisone, and no rise occurred after ACTH administration.

The initial levels of plasma hydrocortisone were below normal in the patients with hypopituitarism (R. P.) and with the adrenogenital syndrome (S. S). Although the levels rose gradually during ACTH infusion, in neither case did they reach normal. Patient E. S. had similarly low plasma levels of hydrocortisone at the start of the study, but she was able to increase her production of this steroid to such an extent that it soon exceeded normal values.

From these studies it was apparent that the patient's low adrenal cortical activity was not due to Addison's disease, since her adrenal cortex could produce steroids. ACTH and exogenous steroids were then withheld and the dramatic events described by Dr. Federman ensued promptly. At the time of this episode of adrenal cortical insufficiency, no hydrocortisone could be detected in her plasma. This failure to maintain production of adrenal steroids after ACTH was withheld seemed to rule out the possibility that her poor adrenal function was due to suppressed production of ACTH by the pituitary gland secondary to the use of prednisone and hydrocortisone. In such situations, the production of endogenous adrenal steroids is usually maintained after cessation of exogenous ACTH administration.

We are left, then, with the diagnosis of interference with the activity of the pituitary gland or the hypothalamus by an internal process, probably a metastatic lesion. You will recall, however, that graphs of the studies performed on the patient (figures 1, 2 and 3) resembled normal results more closely than did those obtained in studies of a patient with classic hypopituitarism. This discrepancy may be due to the fact that her pituitary failure was of short duration and she had not yet developed the atrophied adrenal cortices usually found in patients with long-standing hypopituitarism.

Dr. Bunim: We are privileged to have Dr. David Barr to discuss this case and correlate the clinical and anticipated morphologic findings.

Dr. Barr: It is a great privilege to be here and also to discuss this extraordinarily interesting patient. You have already heard a careful review of the history and examinations, and from Dr. Federman a fine analysis of the various factors which contribute to an understanding of this case. I think it is worth while, however, to review the story so that we may, if possible, place ourselves in the position of those who actually saw the patient and point out any justifiable inferences.

You have heard that this woman had a breast cancer which could not be completely removed, and that 10 months later she developed diabetes insipidus. This immediately suggests that in some way she developed a lesion in the hypothalamus or the region of the pituitary stalk or the pituitary sella. It is possible that the diabetes insipidus may have developed from functional changes, but the circum-

stances indicate that an organic lesion developed in that location.

Next we hear that she had three attacks of pneumonia in rapid succession between 10 and six months prior to her admission here. The circumstances of the pulmonary involvements are not well defined, but when a patient develops three attacks of so-called pneumonia within a few months it is usually indicative of some chronic lung disease. This may, of course, be an obstructive lesion, perhaps from a carcinoma of the lung. Such repeated attacks of pneumonia may come from other chronic diseases: bronchiectasis, chronic fibrosis or, very rarely,

metastatic carcinoma of the lung.

When she had her third attack of pneumonia it was discovered that she had adrenal insufficiency, and Dr. Peterson very nicely defined the questions that would have been asked at that time. Was this a primary adrenal disease, a true Addison's disease, in which both adrenal cortices would be completely or partially destroyed? Or was this just another manifestation of some organic lesion in the region of the pituitary gland? You can imagine that those who observed this case before admission to the National Institutes of Health were swaved by a test in which ACTH was given and no evidence of adrenal stimulation developed. So, within the limits of the test and within the limits of the understanding of the case at that time, there might have been a justifiable conclusion that this woman actually did have Addison's disease. It was interesting that she was given prednisone and/or hydrocortisone first and that she improved, but this does not, of course, differentiate at all between a primary adrenal insufficiency and one secondary to pituitary disease. It was recognized that when prednisone was withdrawn she rapidly developed an addisonian crisis, with hypotension, fever and semicoma.

In the four months preceding her admission to the National Institutes of Health she developed some new signs and some revealing symptoms. She had headaches to which she had not previously been subject. She also suffered cold intolerance and puffiness of the eyes, which might indicate a hypothyroidism. Some of her symptoms at that time were not very helpful in the diagnosis, and I don't know how to explain them. She complained of blurring vision and mentioned a special blurring in the inferior quadrant of both visual fields. This occasionally occurs when there is an obstructive lesion in the internal carotid arteries, but it is not at all revealing of a change in the sella turcica.

She complained of numbness and burning of her throat,—symptoms that I am unable to relate to the rest of the picture. She had difficulty in breathing,

and at that time exhibited signs of Cushing's syndrome resulting from prednisone administration.

There are other items in her history that might have attracted attention. One was that she was pregnant at the age of 30. She bled a great deal and was ill after her miscarriage, which suggests a possible obstruction of the artery to the pituitary gland, and production of Simmonds' disease. But all this happened so long ago that one doesn't relate it to the circumstances of the present illness. Then at the age of 47, five years before she came here, her uterus and ovaries were removed.

I don't think the physical examination at the time of her admission helped to localize the lesion. She had a "buffalo hump" and a "moon face." She had the dry skin and puffiness of myxedema. Her thyroid gland was not felt. Her right breast was absent, and there were some nodules that may have excited a little anxiety but which did not grow under observation. She had sticky respiratory râles in her right base. There was evidence of fibrosis in the bases of her lungs.

This patient had a rather low sodium, and potassium was within normal limits. Her spine was demineralized, but that might have been due to her age and the fact that she had had an artificial menopause.

A pituitary lesion, or one that involves pituitary function and the hypothalamus, might arise from a tumor in the sella turcica, but if present it did not disturb the outlines of the sella.

You have been told of the special tests made to confirm the presence of endocrine disease—the Carter-Robbins test, which confirmed the presence of diabetes insipidus; low basal metabolism, low protein-bound iodine, low radio-iodine uptake, all indicative of hypothyroidism; diminution of gonadotropic excretion, indicative of impaired pituitary activity. In a woman who had lost her ovaries, one might expect to have a higher than normal gonadotropin excretion, but in this case there was almost none.

The interesting tests with ACTH which Dr. Peterson discussed proved without any doubt that the function of the adrenal cortex was still excitable, and that its impairment was not due to the prolonged use of corticoids, as it might have been, but was indeed due to lack of stimulation by the anterior lobe of the hypophysis.

You have been told about the final test, in which prednisone was withdrawn and ACTH was not given. A second adrenal crisis (addisonian) developed, which prednisone and other endocrine therapy did not check. In spite of receiving hydrocortisone daily in large amounts and in spite of intramuscular pitressin, she remained lethargic and febrile. She experienced no improvement even after massive intravenous injections of hydrocortisone and ACTH.

In summary, I would say that there is unequivocal evidence of disease of the pituitary gland. The difficulty probably was not in the sella itself, and did not represent a tumor of the pituitary gland, but was above the sella, due either to meningitis or to a space-occupying lesion that was able to interfere with the function of the hypothalamus and, at the same time, interfere with the stalk of the pituitary or the function of the anterior lobe of the hypophysis.

The sequence of events would certainly suggest that this could have been a metastatic lesion from the breast cancer. The great difficulty in accepting this

suggestion is that there did not seem to be metastasis elsewhere, and that the pituitary is not a very common location for a single metastasis. On the other hand, carcinoma of the breast may metastasize anywhere, and it is not inconceivable that a metastatic carcinoma took root there during the 10 months after her mastectomy and caused all the subsequent difficulty.

And then, of course, comes the surprise. The diagnosis of a carcinoma metastasis was not entirely satisfactory. Because this woman had headaches, was doing very badly, and probably because she became comatose and developed a slight ptosis, it was decided to do a spinal puncture. Then it was found that her spinal fluid was under moderately increased pressure, and that it contained 300 red cells and 200 white cells, 50% of which were lymphocytes. Many Torula organisms were found by culture.

After the spinal puncture she developed a stiff neck for the first time. An India ink preparation confirmed the culture, and confirmed, as it almost always does very easily, the presence of these small, discrete, beautifully outlined little

organisms.

About this time treatment became frantic and included intravenous fluids, hydrocortisone, pitressin, penicillin, streptomycin, sulfadiazine, endomycin, noradrenalin and oxygen. In spite of this the patient succumbed. This was on the

sixtieth hospital day.

In this case the unexpected, dramatic discovery of a Torula permits some inferences which tend to make all the symptoms and signs more understandable. When we infer, however, it must be emphasized that we are doing so without proof that Torula actually caused the damage. Torulosis is a disease that has been known for some time. In 1916 Stoddard and Cutler described a case of meningitis which was apparently due to Torula. The organism has been known since 1894. As you probably know, the fungus has a rather wide distribution. It is found in the skin and in the feces of many otherwise normal individuals. It is found in the skin of fruits. It is not very invasive. Indeed, it is regarded as one of the least active mycotic organisms. When it does invade, it can invade anyone from an infant at birth to adults over 70. It affects the skin. Usually it is not diagnosed from skin lesions, but some very interesting ones have been described, such as pustules resembling myxomatosis tumors. It involves the lungs, and sometimes this lung involvement may be asymptomatic, but at other times there are signs of pneumonia. With that, there may be dullness to percussion, râles, and not infrequently the x-rays may show areas of rather dense consolidation. In reviewing this subject I have found very striking x-rays in Conant's Manual of Clinical Mycology and also in an article by Reeves, Archives of Internal Medicine, Volume 68, page 57.

The pathology of these changes in the lungs is varied—fibrosis, an organizing

type of pneumonia, and sometimes cyst formation.

Usually the disease is not recognized by the pulmonary signs and complications, and indeed, when we see typical pneumonias, Torula infection would be one of the last things we would think about. Most of the cases are recognized from a meningeal involvement, and the spinal fluid may contain a number of cells. There may be lymphocytes, elevated proteins and decreased sugar.

The organisms can grow in the brain substance and give rise to focal neurologic signs. One of the curious features of Torula infection is that there is very little cellular reaction about the point of invasion in the brain substance involved. When the meninges are involved there is very little polynuclear formation and only a moderate cellular response. The entire reaction may develop very slowly.

It is interesting that Torula infection does not excite immunity easily. Neal and his associates at Cornell were the first to show an immune reaction to Torula.

In relation to the case under discussion, in which adrenal insufficiency was a prominent feature, it is interesting to note that Torula may invade the adrenal glands. They have been demonstrated on a number of occasions, and in one instance there was destruction of both adrenal glands and the development of a true Addison's disease. This was a case reported by Rawson in the American Journal of Medical Sciences, Volume 215, page 363.

The pituitary gland may also be involved. Ischemia of the anterior lobe of the pituitary was reported in one instance, with resulting pituitary insufficiency. If the case under discussion today represents pituitary insufficiency secondary to Torula disease of the pituitary gland, it will be the second case reported.

To summarize again, this is the story of a woman who had a carcinoma of the breast which could not be completely removed but did not demonstrably metastasize. It is the story of a woman who at some stage in her disease developed an infection with Torula. It seems possible that this infection, through ischemia or localized meningitis or actual invasion, involved the hypothalamic pituitary region, with resultant diabetes insipidus, pituitary insufficiency, and secondary adrenal insufficiency, hypothyroidism and gonadotropic deficiency. It also seems possible that the organism may have involved the lung and may have been responsible for the three so-called attacks of pneumonia. On the other hand, it must be emphasized that the hypothesis of metastases to the pituitary from carcinoma of the breast is not excluded by anything that has appeared in the history.

Dr. Bunim: Thank you, Dr. Barr. Dr. Edgcomb will present the necropsy findings.

DR. EDGCOMB: The major pathologic findings at necropsy include:

1. Diffuse meningitis (Cryptococcus neoformans).

2. Thrombosis, superior sagittal sinus. Massive hemorrhage, right cerebral hemisphere; multiple hemorrhages, left cerebral hemisphere, pons and cerebellum.

3. Replacement of the posterior lobe and most of the anterior lobe of the pituitary gland, by metastatic mammary carcinoma.

4. Necrotizing bronchopneumonia (gram-positive bacteria, Candida, and Cryptococcus seen in sections).

The degree of panhypopituitarism present in a given patient may be reflected in the body weight and in the weight of various visceral organs. In this patient only the spleen and the thyroid gland were unusually small. The spleen weighed 40 gm. and the thyroid gland 6.8 gm. The weights of other organs were: heart, 300 gm.; liver, 1,610 gm.; pancreas, 95 gm.; kidneys, 140 and 160 gm.; adrenal glands, 15.5 gm.; pituitary gland, 0.64 gm. In multiple sections of the pituitary gland the posterior lobe and an estimated three fourths of the anterior lobe were seen to be replaced by metastatic mammary carcinoma (figure 4). No lesions were seen in sections of the hypothalamus. These findings are consistent with

Tune 1957

the clinical history of diabetes insipidus followed by symptoms of anterior lobe insufficiency.

The intracerebral hemorrhages (figure 5), immediately responsible for the patient's death, are associated with thrombosis of the superior sagittal sinus and of the veins of the right parietal area. No metastatic lesions were present in these areas. The right lateral ventricle was filled with clotted blood. The thrombotic process appears to have been the result of extensive cryptococcal



Fig. 4. Anterior lobe, pituitary gland, extensively replaced by metastatic carcinoma of the breast. Hematoxylin-eosin stain.

meningitis (figure 6). The choroid plexuses and the ependymal surfaces contained cryptococci, and the lateral recesses of the fourth ventricle were filled with exudate and organisms.

Cryptococcal disease in the lungs was limited to a microscopic subpleural lesion in the right lung (figure 7). Elsewhere in the lungs there was extensive necrotizing bronchopneumonia.

Metastases from the breast carcinoma were found in the liver, lungs, mediastinal lymph nodes, right axilla, retroperitoneal lymph nodes, deep cervical lymph

nodes and pituitary gland. The metastases were small; the weight of carcinomatous tissue present in the entire body was estimated to have been less than 50 gm.

At necropsy, metastatic lesions of the pituitary gland have been observed frequently in patients with carcinoma of the breast.² One of Simmonds' cases was a cachectic woman whose pituitary gland had been destroyed by carcinoma metastatic from the breast.³ The pituitary gland replaced by metastatic carcinoma is often reported to be of normal size. Metastases to the posterior lobe occur more frequently than metastases to the anterior lobe. Systemic effects



Fig. 5. Massive hemorrhage, right cerebral hemisphere. In addition, there is inflammatory thickening of the fragments of meninges adherent to the superior medial aspect of the brain.

associated with pituitary metastases include diabetes insipidus, emaciation and glycosuria.4

It is remarkable that the pituitary gland of this patient should have been so extensively replaced at a time when other metastases were small.

DR. UTZ: Most patients with cryptococcosis have very few and oftentimes misleading symptoms. None of the five patients we saw in the past year had a stiff neck. Two of them are alive and, in fact, returned to work within 18 months after the diagnosis was made. As you may be aware, some patients with the disease do very well and may survive more than 10 years with the infection.

Torula meningitis is not an uncommon complication of lymphoma, especially of Hodgkin's disease, and in the care of such patients the possibility of Torula meningitis must be kept in mind.

Dr. Barr commented on the invasiveness of these organisms. We had a patient in whom the aortic and mitral heart valves had been invaded. In other cases one may find involvement of the lungs, adrenal glands, kidneys, bone, thyroid gland, lymph nodes and prostate.



Fig. 6. Cryptococcal meningitis. The cryptococci are visible as round black bodies. Gomori's methenamine silver stain.

The epidemiology of cryptococcosis is of interest. None of the cases reported indicated spread from man to man, and there is no reason to suspect it is spread from animal to man. In 1951 Dr. Chester W. Emmons, of our Institute, discovered cryptococci in the soil, and later he observed that these organisms were more common when pigeons were present in the environment. Following this, he investigated farm areas where pigeons were common, and in many of these he was able to isolate cryptococci from the soil. This is an important lead in deter-

mining the transmission of the disease and is worth further study. Pigeons, incidentally, are not infected.

My final comment concerns treatment of the meningitis in this case. At present, there is no known effective treatment for cryptococcosis. We have tried a number of compounds without success. We hope a drug will be found eventually that can cure this disease.



Fig. 7. Cryptococcal pneumonitis, right lung. This small subpleural mucoid focus situated lateral to the small bronchus is the only cryptococcal lesion demonstrated in the lungs. Hematoxylin-eosin stain.

DR. RALL: When I first saw the patient I was asked why there was 24% uptake of 1¹³¹ if the patient had hypothyroidism. She looked hypothyroid, and she had a protein-bound iodine of 2.2 µg.%, a serum cholesterol of 333 mg.% and a basal metabolic rate of minus 18%. One must consider the 24% iodine uptake in terms of the mean value which, as determined at the National Institutes of Health, is in the range of 35%. Furthermore, patients with clinical hypopituitarism may have an appreciable iodine uptake by their thyroid, ranging from 10 to 25%. This is in contrast to patients from whom the pituitary has been

completely removed surgically. The iodine uptake values in such subjects are less than 5%.

It is of some interest that this woman probably developed the metastasis to the pituitary at least 10 months before she was admitted, when she developed her diabetes insipidus. In spite of the metastasis in her lungs, she continued for 10 months with little apparent progression. I am wondering if perhaps, contrary to Dr. Edgcomb's comments, she may have been fortunate to have had a metastasis in the pituitary. It is conceivable that the hypophysectomy which she performed on herself eliminated growth hormone and thereby may have ameliorated her neoplastic disease.

Dr. Barr: I have found this case extremely instructive. There is one very small point that interested me. I spoke about the relationship of obstructive pulmonary lesions to repeated episodes of pneumonia. Certainly everyone who has seen many primary bronchogenic carcinomas has been struck by the frequency of a previous history of repeated attacks of so-called pneumonia. I had occasion to comment that a metastatic carcinoma seldom does that. I found it rather interesting that there was a metastasis in this patient, which was obstructing a bronchus, and which may have exerted partial obstruction, thereby permitting the formation of temporary pulmonary infection distal to it.

SUMMARIO IN INTERLINGUA

Un femina de 52 annos de etate esseva admittite al hospital pro studios del metabolismo steroide. Vinti menses previemente un mastectomia radical al latere dextere habeva revelate metastases carcinomatose non accessibile al dissection. Intraun anno ante le admission al hospital, diagnoses de diabete insipide e de insufficientia adrenal esseva facite. Le insufficientia adrenal non respondeva al therapia de reimplaciamento steroide. Habeva etiam occurrite mal de capite, tumescentia circa le oculos, e tres episodios de pneumonia. Le tertie de istos non habeva respondite a penicillina. Le examine physic revelava un facie "lunar," pronunciate gibbositate de buffalo, e normal corde, pulmon, abdomine, e area pelvic. Varie studios roent-genographic non revelava metastases, ben que signos de fibrositate esseva notate al bases pulmonar. Le delineation del sella turc esseva normal. Le test de Carter-Robbins confirmava le presentia de diabete insipide. Tests del metabolismo basal e del acceptation de iodo pareva indicar hypothyroidismo. Diminuite valores del excretion gonadotropic indicava un disordine del activitate pituitari.

Es describite in detalio como le function adreno-cortical del patiente esseva evalutate per determinar le excretion urinari e le concentration plasmatic de corticosteroides durante un periodo de 72 horas de un continue infusion intravenose de ACTH. Le patiente habeva basse valores initial del rendimento de 17-cetosteroides, sed istos cresceva durante le periodo de 72 horas de maniera significative. Le excretion de corticosteroides cresceva ab nivellos infranormal a nivellos normal. Le nivellos plasmatic de hydrocortisona cresceva ab nivellos infranormal a nivellos supranormal. Esseva concludite super le base de iste studios que le basse activitate adreno-cortical non esseva un effecto de morbo de Addison, viste que le cortice adrenal esseva capace a producer steroides.

ACTH e steroides exogene esseva abstenite, e le patiente disveloppava promptemente signos e symptomas de insufficientia adrenal. Esseva concludite que un lesion metastatic habeva impedite le activitate del glandula pituitari sed que iste occurrentia esseva si recente que le atrophiate cortice adrenal—ben que su function esseva infra le nivello normal—respondeva ancora al stimulation per corticotropina exogene.

Ben que debile e allectate, le patiente se sentiva melio e habeva un aere meliorate quando le therapia de reimplaciamento de ACTH esseva re-instituite. Culturas de fluido spinal—obtenite per punctura lumbar a causa del persistente lethargia e mal de capite—produceva abundante colonias de Torula. Gradualmente le patiente entrava in coma e stato de choc e moriva le sexantesime die de su hospitalisation.

Le principal constatationes necroptic esseva (1) meningitis diffuse (Cryptococcus neoformans), (2) thrombosis e hemorrhagias multiple del cerebro, (3) reimplaciamento quasi complete del glandula pituitari per metastatic carcinoma mammari, e (4) bronchopneumonia necrotisante (bacterios positive al Gram, Candida, e Cryptococcus vidite in sectiones).

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CASE REPORTS

CHLORPROMAZINE HEPATITIS TREATED WITH CORTISONE *

By Morgan Cutts, M.D., F.A.C.P., Providence, Rhode Island

The occurrence of jaundice following chlorpromazine therapy has been repeatedly noted, but the exact mechanism of its production remains in doubt.^{1, 2} Some authors suggest a drug sensitivity, others an increased viscosity of the bile produced by the medication. Recently, benefit from treatment with cortisone in one case has been reported.¹ Following is a report of another such case.

CASE REPORT

A 45 year old woman was admitted to the hospital because of increasing anorexia, nausea, weakness and epigastric distress for 10 days. For one week she had noted increasingly dark urine and severe generalized pruritus. She had taken 25 mg. of chlorpromazine three times daily for the two weeks immediately prior to the onset of her present illness. Five months before admission she had undergone a hysterectomy for uterine fibroids and endometriosis, and had received a pint of whole blood at that time. She had had no fever or chills.

On admission temperature was 98.6° F.; pulse, 86; respirations, 20; blood pressure, 120/70 mm, of Hg. The patient was well developed and well nourished. The skin and sclerae were slightly icteric, and there were scratch marks over the body. There were slight epigastric tenderness and a well healed lower midabdominal scar. The liver edge was palpable at the costal margin and was not tender. There were no other masses, and the remainder of the physical examination was normal.

The red blood cells were 4.8 million; hemoglobin, 14.6 gm.; white blood cells, 7,000, with polymorphonuclear neutrophils 44%, lymphocytes 37%, monocytes 3%, eosinophils 14%, and basophils 2%. The urine showed a specific gravity of 1.012; pH, 6; protein and sugar, negative; sediment, normal; bile, strongly positive; urobilingen, 0.08 mg./100 c.c. Van den Bergh reaction was 3.1; thymol turbidity, 4; cephalin flocculation, negative; alkaline phosphatase, 12.7 K.A. units; total serum protein, 7.2 gm.; albumin, 4.5 gm. Two days after admission the patient was started on cortisone, 25 mg, four times a day. Following this there was marked improvement in her appetite, her pruritus cleared dramatically, and steady subjective improvement began. A week after admission repeated urine examination showed bile only weakly positive; van den Bergh, 1.6; alkaline phosphatase, 9.3 K.A. units; thymol turbidity, still 4. The white blood cell count was 9,700, with polymorphonuclear neutrophils 45%, lymphocytes 50%, and eosinophils now only 4%. The patient was discharged from the hospital, and cortisone was gradually discontinued over the next four days. One week later she was feeling well, and bile was no longer present in the urine.

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SUMMARY

This case is presented as an instance of chlorpromazine hepatitis that was promptly benefited by cortisone therapy. If this proves to be the general finding, then short-term steroid therapy with its low risk of side-effects would certainly be indicated in most cases. The definite eosinophilia is of interest in connection with the possible role of sensitivity in the etiology of the condition.

SUMMARIO IN INTERLINGUA

Le occurrentia sporadic de jalnessa post cursos de chlorpromazina es ben cognoscite. Un femina de 45 annos de etate disveloppava jalnessa post prender chlorpromazina durante duo septimanas. Illa esseva afebril, e su hepate esseva palpabile. Post therapia con cortisona, le signos e symptomas de jalnessa se resolveva promptemente.

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ADRENAL INSUFFICIENCY PRODUCED BY METASTASES FROM GASTRIC CARCINOMA*

By Olga Cushing Leary, Jr., M.D., and Jacob J. Masters, M.D., Chelsea, Massachusetts

CASES of adrenal insufficiency produced by metastatic carcinoma are unusual, if not rare, though carcinomatous metastases to the adrenals are not uncommon. The obvious explanation is probably the correct one—that patients usually die as the result of the primary lesion or of metastases to other organs, before the adrenal metastases attain great size or destructiveness. Bronchogenic carcinoma is notably prone to produce adrenal metastases, and a number of well documented cases of adrenal insufficiency resulting from such metastases have recently been published.^{1, 2} It may be of interest to add another case to the much smaller series of primary gastric carcinomas with adrenal metastases and adrenal insufficiency.

CASE REPORT

A 60 year old white male was admitted to the Soldiers' Home Hospital, October 27, 1952, because of constant epigastric pain, nausea and vomiting of seven weeks' duration. During this period the patient had become anorexic and had lost 30 pounds.

* Received for publication January 17, 1956.
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The patient had a long history of emphysema and respiratory distress. He had been admitted to a Veterans Hospital in 1945 for treatment for respiratory disease, and at this admission a diagnosis of chronic duodenal ulcer was made. In 1949 he was admitted to another Veterans Hospital and was discharged after a month with diagnoses of active peptic ulcer, probably duodenal, and emphysema. Following this the patient remained fairly well, with only minor intermittent attacks of epigastric pain, until the

onset of the present illness.

The notable physical findings on admission were light brown pigmentation of the skin of head and neck, a blood pressure of 120/70 mm. of Hg, a tender liver palpable four fingerbreadths below the costal margin, and epigastric tenderness. The skin pigmentation, in conjunction with the gastrointestinal symptoms and hypotension, suggested the possibility of adrenal insufficiency. A control eosinophil count on November 6 was 300 per cubic millimeter; four hours after the administration of epinephrine the eosinophil count was 270 per cubic millimeter. The 24-hour urinary 17-ketosteroids were 1.4 mg. on November 7. A skin biopsy from the affected area confirmed the increase in epidermal pigmentation, and failed to show iron on special stain. X-ray studies of stomach and duodenum were interpreted as antral gastritis and chronic duodenal ulcer. On November 4 the patient first complained of back pain, which persisted thereafter. On November 8 yellowing of the sclerae was first noticed; by November 10 frank jaundice was apparent, and this increased steadily. On November 13 the cephalin flocculation was negative; thymol turbidity, 1 unit; alkaline phosphatase, 38.9 units; albumin, 4.5, and globulin 3.5 gm.%. A liver biopsy on November 21 showed cholangitis and bile stasis. The patient's condition continued to deteriorate. Hypotension became more marked, the pressure ranging between 100/60 and 84/38 mm. of Hg. The most probable clinical diagnosis was felt to be carcinoma of the pancreas with extrahepatic biliary obstruction and adrenal metastases. The patient was transferred to the surgical floor for possible exploratory laparotomy, but died 48 hours later, on December 1.

At autopsy the skin of the head and neck was noted to be the color of copper, while the remaining skin was jaundiced. A large (4.5 by 5.5 cm.), shallow ulcer was found just proximal to the pylorus. Solitary metastatic nodules occurred in the left lower lobe of the lung and the spleen. There were a few small liver metastases, and large metastases in the peribronchial and peripancreatic nodes. The left adrenal measured 8.5 by 5.5 by 2.5 cm., and the right adrenal 6.5 by 4 by 1.7 cm. Both on

gross examination appeared to be entirely replaced by neoplastic tissue.

Microscopically the lesion appeared as a rather poorly differentiated carcinoma which infiltrated the entire thickness of the gastric wall and appeared in the perigastric fat. Sections from both common and cystic ducts showed infiltration of the muscularis and the lamina propria with tumor. The liver showed an early biliary cirrhosis. The metastatic neoplasm in the adrenals was slightly better differentiated than the primary lesion and showed some acinus formation. While adrenal tissue was largely destroyed, tiny scattered islands of cortical cells remained.

DISCUSSION

A rather rapid check of the literature since 1900 shows only four published cases of adrenal insufficiency produced by metastases from gastric carcinoma. In the first of these, reported by Straub ³ in 1909, the patient had obvious malignant disease, with the sudden development of asthenia, hypotension, and characteristic pigmentation in the 10 days before death. The adrenal metastases were of only moderate size, but extensive venous thrombosis resulting from the metastatic involvement was believed to have caused the symptoms of adrenal

insufficiency. In the second case, reported by Spangenberg * in 1928, the gastric carcinoma was silent; the patient entered the hospital in extremis, with a history of increasing skin pigmentation and weakness during the preceding year, and died within 24 hours of admission. The adrenals showed medullary metastases with cortical distortion on one side. The third case, reported by Madheim * in 1941, also had a silent gastric carcinoma and was thought clinically to be a case of subacute bacterial endocarditis. Pigmentation was not present, but the patient had muscular weakness, anorexia, apathy and profuse sweating. Autopsy showed multiple bilateral adrenal metastases, with plugging of veins and extensive hemorrhagic necrosis, and the case was considered in retrospect to be one of Addison's disease. Lastly, Butterly et al.¹ reported a case in 1952 which they regarded as unproved, since laboratory work had not been completed at the patient's death. However, the patient had pigmentation, asthenia, nausea and vomiting and hypotension; part one of the Robinson-Power-Kepler water test was positive, and autopsy showed extensive bilateral adrenal metastases.

Published statistics give the over-all frequency of adrenal metastases in cases of carcinoma as ranging from 9% 6 to 13%. The autopsy records of the Soldiers' Home Hospital for the five-year period 1950 through 1954 show 82 cases of carcinoma with 27 adrenal metastases, a frequency of 32.9%. The distribution of primary sites in the cases with adrenal metastases, and the frequency, are shown in the following table:

TABLE 1

		Adrenal Metastases	
	Number of Cases	Unilateral	Bilateral
Lung	17	8	3
Large bowel	17	5	_
Stomach	13	2	3
Thyroid	2		1
Melanocarcinoma	1		1
Other sites	4	4	

Butterly et al.¹ suggest that adrenal insufficiency produced by metastases may be masked by the cachexia of advanced malignant disease. The Soldiers' Home Hospital autopsy records tend to support this view, since, excluding the presently reported case, they show three other cases of extensive bilateral adrenal involvement by metastatic carcinoma. None of these patients showed pigmentation or was considered clinically to have Addison's disease. One of them, a case of melanoma, received ACTH without benefit. Autopsy showed complete gross and microscopic destruction of the adrenals. In the other two cases, one primary in the thyroid, and one in the stomach, a very little residual adrenal cortex was found.

It is no doubt worth while to investigate adrenal function in patients with malignant disease, since if diminution or absence of adrenal function is demonstrated, therapy may increase comfort, if not prolong life. It is also worth remembering that, while carcinoma of the lung is unquestionably the chief offender in producing adrenal metastases, with or without resulting insufficiency, other carcinomas also frequently metastasize to the adrenals and may be sufficiently destructive to inhibit adrenal function.

SUMMARY

Metastatic carcinoma in the adrenals is fairly common, but patients usually die before the adrenal lesions become sufficiently destructive to produce symptoms of adrenal insufficiency. While carcinoma of the lung is the primary lesion which most frequently produces adrenal metastases and has caused the greatest number of reported cases of Addison's disease due to neoplasm, carcinoma of the stomach has been recorded as causing adrenal insufficiency four times since 1900, and the present case adds a fifth to this series. The autopsy records of the Soldiers' Home Hospital tend to bear out the contention that more cases of adrenal insufficiency caused by metastatic carcinoma would be uncovered if studies of adrenal function were undertaken in patients with malignant disease, since the records for the years 1950 through 1954 show three cases of massive bilateral adrenal destruction, exclusive of the present case.

SUMMARIO IN INTERLINGUA

Casos de insufficientia adrenal producite per carcinomas metastatic es inusual si non rar, ben que metastases carcinomatose al adrenales non pote esser considerate como incommun. Le plus obvie explication—e probabilemente le explication correcte—es que le patientes mori usualmente in consequentia del lesion primari o in consequentia de metastases a altere organos ante que le metastases adrenal pote devenir grande o multo destructive. Durante que carcinoma del pulmone es le lesion primari que causa le plus frequente metastases adrenal e que ha producite le plus grande numero del reportate casos de morbo de Addison, le litteratura depost 1900 cognosce quatro casos de morbo de Addison causate per carcinomas gastric. Le presente reporto adde un quinte caso a iste serie.

Il se tracta del caso de un masculo blanc de 60 annos de etate qui esseva admittite al hospital a causa de constante dolores epigastric, nausea, vomito, anorexia, e un perdita de quasi 14 kg de peso. Le symptomas habeva durate septe septimanas. Le examine del patiente monstrava un pigmentation clar brun del pelle de capite e collo. Al tempore del hospitalisation le pression sanguinee esseva 120/70 mm Hg sed descendeva subsequentemente a inter 100/60 e 84/38 mm Hg. Le numeration eosinophilic descendeva levemente post administration de epinephrina. Le 17-ceto-steroides urinari pro 24 horas esseva 1,4 mg. Le curso del morbo esseva marcate per un deterioration rapide, e le morte del patiente occurreva 35 dies post su admission al hospital.

Al necropsia le adrenales se monstrava grandemente allargate. Lor tessuto specific esseva apparentemente reimplaciate in toto per le crescentia neoplastic. Esseva presente un ulcere carcinomatose del stomacho.

Es opinate que plus numerose casos de insufficientia adrenal causate per carcinoma metastatic esserea discoperite si studios del function adrenal esseva interprendite in patientes con maligne morbos. Le archivos del Hospital Memorial Lawrence F. Quigley a Chelsea in Massachusetts pro le annos ab 1950 usque al fin de 1954 contine le dossiers de tres casos de massive bilateral destruction adrenal per carcinomas, sin contar le caso del presente reporto.

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PHEOCHROMOCYTOMA ASSOCIATED WITH PAINLESS MYOCARDIAL INFARCTION *

By Martin H. Boldt, M.D., F.A.C.P., Morris Flexner, M.D., F.A.C.P., and Alvin B. Ortner, M.D., F.A.C.S., Louisville, Kentucky

More than 300 cases of pheochromocytoma have been reported since Labbe, Tinel and Doumer 1 in 1922 first described the clinical picture in its hypertensive paroxysms. About 0.5% of all patients with hypertension are thought to have a functioning chromaffin tumor,3,4,5 and it is estimated that between 600 and 800 people die annually from this cause.⁵ These deaths are preventable, for the hypertension due to this tumor is curable. The clinical features of this disease, as well as the various diagnostic procedures, have been adequately described.2, 6, 7, 8, 9, 10, 11, 12, 18, 14, 15, 16, 17, 18, 19, 20, 21, 22 In spite of this, there are probably more unrecognized deaths annually from this ailment than there are case reports in the literature. This is due to the great variability of the clinical picture, and the fact that the diagnostic methods commonly employed have many shortcomings both in the response by the patient 9, 18, 20, 28, 24, 25, 26, 27 and in the interpretation by the physician. 28, 29, 30, 81, 82, 83 The hypertension may be either sustained or paroxysmal; however, the association of hypertension with episodes of excessive sweating, throbbing headaches and other vasomotor phenomena, and with hypermetabolism and glycosuria, should make one consider the possibility of a pheochromocytoma.

A number of investigators have demonstrated increased amounts of vasopressor material in the blood and urine of patients with pheochromocytoma, but these technics are difficult to apply routinely.^{13, 34, 35, 36} More recently, Goldenberg and his collaborators have devised a relatively simple laboratory test for the determination of urinary catecholamines.³⁷ These workers, as well as others,³⁸ have demonstrated that patients with functioning chromaffin tumors excrete much more catecholamine in their urine than do normal individuals or patients with hypertension from other causes.

^{*} Received for publication January 23, 1956.

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The incidence of acute myocardial infarction in patients with pheochromocytoma is unknown. Priest reported such an individual with a fatal outcome. Roseman 40 recently reviewed the problem of painless myocardial infarction and found that it occurred in 4% of his series. This paper is presented because of the interesting association of a painless acute myocardial infarction in an individual suspected of having a pheochromocytoma and manifesting a number of uncommon but apparently related features of functioning chromaffin tumors. The use of the usual pharmacologic agents for diagnosis was contraindicated in this patient because of the recent myocardial infarction. Diagnosis was established by the method least disturbing to an ill patient, the quantitative determination of catecholamines excreted in the urine.

CASE REPORT

The patient, a 56 year old white woman, was admitted to the Norton Memorial Infirmary on October 17, 1953, complaining of weakness and lightheadedness when in the upright position. Since 1940 she had repeatedly experienced severe headaches which were generalized but followed no definite pattern. Since 1948 she is known to have been moderately hypertensive, with blood pressures varying from 152 to 174 mm. mercury systolic and from 74 to 100 mm. diastolic. Her fundi, which in 1948 were normal, in 1949 revealed narrow arterioles with areas of spasm; the arteriovenous compression was marked, and there were many very small, superficially located retinal hemorrhages. In each macula were yellowish, hard, well circumscribed exudates arranged in a radiating or star-shaped fashion. Several larger accumulations of less well circumscribed yellowish exudate were also present in the right eye. A moderate degree of albuminuria and an occasional granular cast had been noted in 1949 and in 1951. In 1948 the patient had a subtotal thyroidectomy. The resected thyroid tissue revealed a diffuse colloid goiter; no lymphoid follicles or lymphocytic infiltration was present. Her metabolism was elevated, and the preoperative basal metabolic rate was plus 75%. The clinical diagnosis was hyperthyroidism. Following this surgery her headaches did not recur. For at least 15 years she has had numerous sessile and papillomatous fleshy tumors over her face and trunk, the largest of which measured 5 mm. in diameter.

Five weeks prior to admission the patient experienced recurrent weak spells. These were characterized by a sudden onset of dizziness and a feeling as if she were going to faint. They were associated with an aching pain in the lumbar region and palpitation. These episodes lasted only a few minutes and were accompanied by a sense of fear. An electrocardiogram (figure 1A), obtained on September 19, 1953, revealed an occasional premature auricular contraction but was otherwise within normal limits. It was thought that these syncopal episodes were related to runs of premature contractions, and the patient was given quinidine; however, these attacks continued to recur. On the day of admission to the hospital she awakened at her usual hour after a restful night's sleep. On assuming a sitting position she became dizzy and had to resume recumbency. Subsequent attempts to rise were likewise unsuccessful because of lightheadedness and weakness. She experienced no pain or shortness of breath.

Physical examination revealed a thin, pale, afebrile, alert woman lying quietly in bed. She was tense but in no apparent distress. Her skin was warm and excessively moist. Scattered over her face, trunk (figure 2) and upper extremities were numerous fleshy tumors as described above. Examination of the heart revealed a short, harsh, grade I systolic murmur at the apex. Her pulse was 110 and her blood pres-

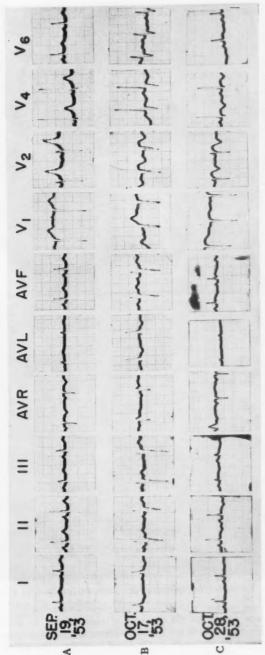


Fig. 1. Electrocardiograms obtained (A) September 19, 1953; (B) October 17, 1953; (C) October 28, 1953.

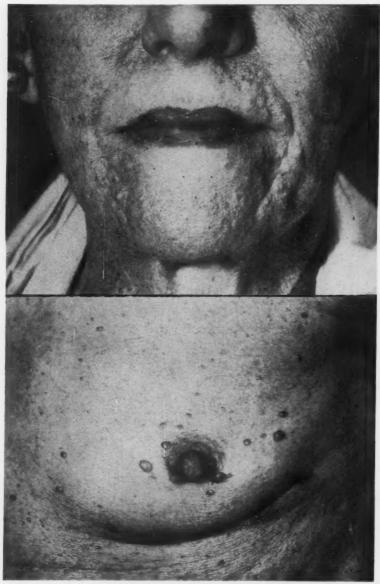


Fig. 2. Neurofibromatosis of face and trunk.

sure in the recumbent position was 110 mm. mercury systolic and 60 mm. diastolic. The lungs were clear except for the presence of some adventitial sounds over the left hemithorax. No masses were felt in the abdomen, and vigorous palpation in the upper quadrants caused no alteration in the blood pressure. On sitting up she be-

came syncopal and was returned to a recumbent position before a blood pressure determination was obtained.

Laboratory Data: The initial urinalysis showed a specific gravity of 1.030 and 3 plus albumin, and the sediment was loaded with leukocytes. Subsequent examinations of the urine revealed a persistent 2 and 3 plus albumin and a few leukocytes. Hemogram on admission was normal except for 11,900 leukocytes. Nonprotein nitrogen was 61 mg. %. Fasting blood sugar was 129 mg. %. An electrocardiogram obtained on the day of admission (figure 1B) revealed ST and T wave changes consistent with a recent anteroseptal myocardial infarction. Subsequent electrocardiograms revealed the expected changes of a recent anteroseptal infarction, and a tracing obtained on the twelfth hospital day (figure 1C) revealed changes consistent with diaphragmatic wall infarction, the second painless infarction in approximately two weeks.

The patient was treated for myocardial infarction with bed-rest, sedatives and anticoagulants. On October 22, 1953, the fifth hospital day, she had a sudden onset of weakness and palpitation. When seen during this episode she was perspiring profusely and her blood pressure was 230 to 240 mm. mercury systolic and 140 to 150 mm. diastolic. Thereafter, and until celiotomy on November 19, 1953, it varied from 102 mm. mercury systolic to over 200 mm. These rises in blood pressure at times persisted for two, three and four days, and usually were not associated with subjective evidence of hyperepinephrinism.

Urinary catecholamine determinations on a 24 hour specimen, collected November 1, 1953, were obtained through the courtesy of Dr. Marcel Goldenberg, of Columbia University. The urine was positive for pheochromocytoma by the short screening method, and this was confirmed by the more accurate quantitative procedure, which revealed the presence of 460 μ g, norepinephrine equivalent. Goldenberg has observed that 100 μ g, norepinephrine equivalent is the highest value observed in cases of essential hypertension. An intravenous urogram obtained on November 10, 1953, revealed satisfactory excretion of the radiopaque material bilaterally. The collecting structures of the kidneys were well shown and were normal. There was no evidence of a mass distorting or displacing the kidneys.

The operation was performed on November 19, 1953. Under general anesthesia the abdomen was entered through an upper abdominal transverse incision, dividing both rectus muscles. A large spherical mass was found in the retroperitoneal region, superior and medial to the right kidney. The pedicle of this mass was isolated, divided and ligated early in the dissection; so that in subsequent handling vasopressor substances would not be released into the blood stream. Following excision of the mass, the opposite adrenal gland was exposed and found to appear normal. The general peritoneal cavity was then explored. Special attention was given to the paraaortic region and the aortic bifurcation. This exploration proved to be negative for further chromaffin tumors.

The blood pressure during surgery was 120 mm. mercury systolic and 70 mm. diastolic, with minor fluctuations. When the tumor pedicle was clamped the blood pressure fell to 90 mm. systolic and 60 mm. diastolic, but it was rapidly restored to the normotensive range by an intravenous drip of levarterenol * which was continued for two hours and 40 minutes. The blood pressure stabilized at 110 mm. mercury systolic and 70 mm. diastolic. The patient was followed in the recovery room for an additional two hours, and when she was returned to her hospital room four hours and 15 minutes after surgery her blood pressure was 130 mm. mercury systolic and 90 mm. diastolic. In the week following surgery her pressure was labile and varied from 144 mm. to 174 mm. mercury systolic and 86 mm. to 96 mm. diastolic. At the time of discharge from the hospital, on November 29, 1953, the tenth postoperative day, the blood pressure was 166 mm. systolic and 94 mm. diastolic.

^{*} Levophed, Winthrop Laboratories.

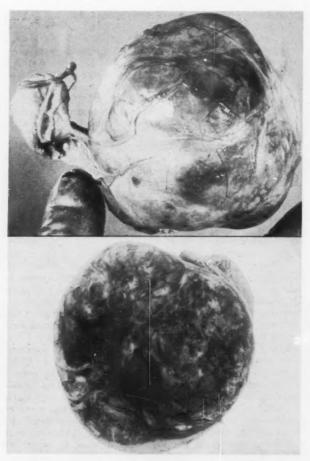


Fig. 3. Pheochromocytoma, capsular and cut surfaces.

Since discharge from the hospital the patient has done well and now feels better than she had for the previous 10 years. The moderate degree of hypertension present at the time of discharge persisted for several weeks and then slowly came down to normotensive levels. In recent months it has been about 110 mm. systolic and 70 mm. diastolic. When last checked, August 8, 1955, the blood pressure was 116 mm. systolic and 68 mm. diastolic, and the pulse was 84. The fundi were completely normal, with no evidence of arteriolar spasm or retinal hemorrhages or exudates.† Her urinalysis revealed no abnormalities.

Pathologic Report: The right suprarenal tumor mass weighed 210 gm. and measured 9.5 by 8.5 by 6.5 cm. (figure 3). The outer covering was shiny, pinkish

[†]This patient's fundi had been examined annually since 1948 by Dr. Kurt Ackermann, an ophthalmologist, who concurs in these findings.

‡The pathologic studies were performed by Dr. Malcolm L. Barnes.

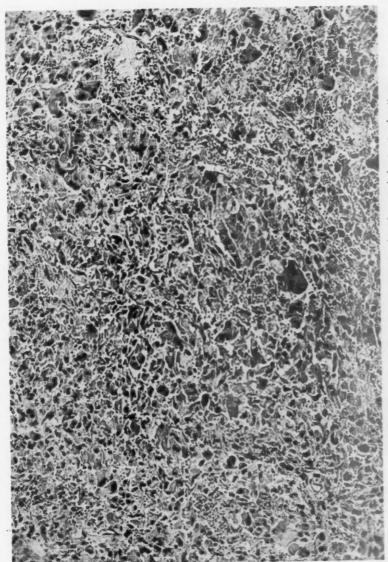


Fig. 4A. H. & E. section of pheochromocytoma showing characteristic structural pattern.

gray, thin and fibrous. The cut surface bulged and revealed several small cystic areas filled with clotted blood. Elsewhere it was bluish gray to pink in color and highly vascularized. Microscopic examination (figure 4A) revealed a diverse cellular pattern. The predominant cells were large, and many were multinucleated. In outline the cells varied from polyhedral to fusiform or spherical, depending upon the plane of the section. The cytoplasm was abundant and slightly granular, containing pigment granules which resembled hemosiderin. The nuclei varied from a central to an ec-

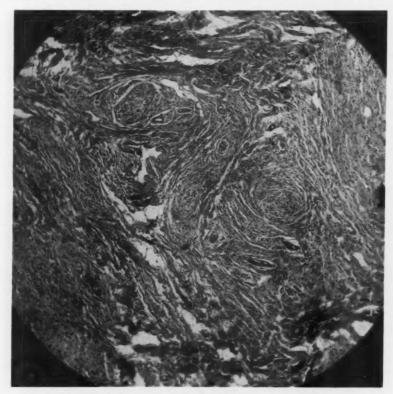


Fig. 4B. Low power magnification of cutaneous neurofibroma.

centric position. Many were vesicular. Bizarre nuclear forms were present, but very few mitoses. Tumor cells were present in several of the many vascular spaces. There was also beginning infiltration of the capsule by these cells.

Sections of one of the fleshy cutaneous tumors (figure 4B), removed during surgery, revealed a small polypoid mass covered by normal appearing epidermis, its body made up of loose connective tissue. In the base there were several small nerve trunks, and about these trunks there was a fairly well circumscribed tumefaction made up of swirling, spindle-shaped cells that showed some streaming and palisading of their nuclei. This cellular pattern is consistent with neurofibromatosis of the skin (von Recklinghausen's disease).

The pheochromocytoma was assayed by Dr. Marcel Goldenberg and revealed 6.35

mg. norepinephrine per gram of tumor tissue, and 1.55 mg. epinephrine per gram of tumor tissue.

DISCUSSION

The diagnosis of pheochromocytoma was entertained when this patient entered the hospital because of the syncopal episodes and because the cutaneous lesions were thought to be neurofibromata. Five per cent of patients with multiple cutaneous neurofibromata and hypertension have pheochromocytoma. Conversely, the incidence of neurocutaneous syndromes among patients with pheochromocytoma is estimated to be about 10%. 19, 41-44

The electrocardiographic findings of a recent myocardial infarction in this patient were unexpected. No pain or temperature elevation was associated with her clinical course at any time prior to surgery. An electrocardiogram obtained five weeks before admission to the hospital was normal except for the presence of an occasional premature auricular contraction (figure 1A). The hypotensive blood pressures and almost continuous excessive perspiration present during the first three days in the hospital were probably on the basis of the recent myocardial infarction. Postural hypotension on the morning of her hospital admission is indeed the reason this patient sought medical attention. Postural hypotension and postural tachycardia may have been due to the myocardial infarction; on the other hand, these symptoms have been recognized as characteristic of some patients with pheochromocytoma in the absence of myocardial infarction.⁴⁵ It is known that this patient had arteriolar disease, and it is conjectural whether the postural hypotension induced the myocardial infarction. Electrocardiographic evidence of myocardial ischemia is not uncommon in pheochromocytoma. Subendocardial infarction has been reported following procedures on patients with pheochromocytoma which have provoked a marked pressor response. MacKeith has reviewed the electrocardiographic changes seen during hypertensive attacks in patients with pheochromocytoma.43

The relationship between the arteriolar lesions and the hypertension cannot be ascertained with any degree of certainty, but the clearing of the vascular lesions in the retinal and renal areas and the normotensive blood pressures since surgery, after more than five years of known hypertension, suggest that the hypertension and the vascular lesions were due to the pheochromocytoma. Goldenberg has shown that the hypertension in cases of pheochromocytoma may outlast the presence of the pressor material in the blood for weeks, as was the case with this patient. It is probable that this is due to the vascular changes which are secondary to the hypertension and are slow in clearing. The reversibility of these changes has been demonstrated.

It is of interest to note that this patient had had a partial thyroidectomy in 1948. Many patients with pheochromocytoma have undergone previous thyroid surgery. It is probable that the hypermetabolism was a manifestation of the presence of excessive epinephrine in this patient's circulation, and this would also suggest that the pheochromocytoma was present prior to 1948.

The use of the adrenolytic compounds piperoxan* and phentolamine † for the diagnosis of pheochromocytoma is contraindicated in recent myocardial infarction. These pharmacologic agents are chemically related to the pressor

^{*} Benodaine, Sharp and Dohme.

[†] Regitine, Ciba Pharmaceutical Products, Inc.

amines and have residual sympathomimetic activity which is manifested by their tendency to induce tachycardia and ectopic beats.^{2, 45} For these reasons these agents were not used in this case. The provocative drugs, such as histamine, tetraethylammonium bromide and methacholine,‡ are likewise contraindicated in recent myocardial infarction, and were not used to establish the diagnosis when the patient's blood pressure was in the hypotensive range.

The recent development of a practical technic for the quantitative determination of catecholamine in urine has many advantages. The incidence of false-negative and false-positive results obtained with the use of all of the available pharmacologic agents is considerable, and the threat of untoward side reactions that attends their use is sufficient to suggest caution in their use. It is hoped that these shortcomings will be overcome by the in vitro test determined

on a 24 hour urine collection.

This tumor was moderately large for a pheochromocytoma; however, it is not unusual that this was not visualized on roentgenographic examination. The right kidney was reported as being slightly lower than the left but not abnormally so. This suggested either an extra-adrenal location for the tumor or a small one in the suprarenal areas. It was therefore surprising to find so large a suprarenal tumor at surgery. In part this may have been obscured by the radiodensity of the overlying liver. One wonders whether laminagrams of the right renal area might have demonstrated this tumor preoperatively. Other radiologic technics, including perirenal and retroperitoneal air insufflation, have been successfully used to demonstrate suprarenal pheochromocytomas preoperatively, but were contraindicated in this case because of the patient's precarious condition.

Surgical excision of the tumor was accomplished uneventfully through a transperitoneal approach, using an upper abdominal transverse incision. It is our feeling that this incision has several advantages over the retroperitoneal lumbar approach. Pheochromocytomas are multiple in approximately 10% of the cases, and through a transverse incision both adrenals can be visualized, as well as the para-aortic area explored. A further advantage is that the pedicle is accessible and can be divided early before mobilizing the tumor, thus decreasing the amount of pressor substance liberated into the blood stream and lessening the

chance of a hypertensive crisis.

SUMMARY

 A patient is described who made an excellent recovery following excision of a pheochromocytoma. The surgery was performed within one and one-half months of two painless myocardial infarctions.

2. The associated vascular changes in the renal and retinal areas and the hypertension returned to normal within five months of surgery.

3. The advantages of the transabdominal approach for surgical removal of functioning chromaffin tumors is discussed.

4. The diagnosis of pheochromocytoma was suspected because of the presence of cutaneous neurofibromatosis.

5. The diagnosis was established by the quantitative determination of catecholamines excreted in the urine.

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6. The practical value of the Goldenberg technic of urinary catecholamine determinations is emphasized.

SUMMARIO IN INTERLINGUA

Es estimate que inter 600 e 800 individuos mori annualmente ab pheochromocytoma. Iste mortes es prevenibile, proque le hypertension causate per iste tumor pote esser curate. Le majoritate del casos non es diagnosticate, ben que le aspectos clinic del morbo e le varie methodos diagnostic ha essite describite adequatemente. Le grande variabilitate del tableau clinic e le difficultate de applicar e interpretar le varie methodos diagnostic explica le elusivitate del diagnose. Ha essite monstrate que patientes con functionante tumores chromaffin excerne augmentate quantitates de catecholamina in lor urina. Goldenberg e su collaboratores ha disveloppate un relativemente simple methodo pro le determination quantitative de catecholaminas urinari.

Es presentate le caso de un femina de 56 annos de etate qui esseva admittite al hospital pro studios in re hypotension postural e syncope. Esseva cognoscite que illa habeva essite moderatemente hypertensive depost 1948. Le presentia de pheochromocytoma esseva suspicite a causa del episodios syncopic e a causa del presentia de neurofibromas cutanee. Se dice que cinque pro cento del patientes con morbo de von Recklinghausen e hypertension ha functionante tumores chromaffin. Al tempore del admission del patiente al hospital, provas electrocardiographic de un recente infarcimento myocardial esseva trovate. Isto representava un contraindication contra le use del commumente usate agentes pharmacologic e del altere technicas del diagnose de pheochromocytoma, i.e. le effectuation de injectiones perirenal o presacral de oxygeno. Le diagnose esseva establite per le methodo le minus disquietante pro le patiente: le determination de catecholaminas excernite in le urina in le curso de 24 horas secundo le technica de Goldenberg. Subsequentemente le patiente disveloppava elevationes paroxysmal del pression sanguinee, con periodos de hypertension persistente. Le dece-secunde die del sejorno al hospital un electrocardiogramma exhibiva alterationes compatibile con un secunde infarcimento myocardial acute. Isto esseva inexpectate, proque le patiente non habeva habite dolores a ulle tempore. Post 33 dies de hospitalisation un exploration chirurgic esseva interprendite, e un tumor suprarenal al latere dextere de un peso de 210 g esseva abferite. Immediatemente post le ablation del pheochromocytoma le pression sanguinee del patiente decresceva. Isto esseva contrariate per le inguttation intravenose de norepinephrina durante duo horas e 40 minutas, usque le pression sanguinee se monstrava stabilisate. Le die post le operation, le patiente habeva moderate grados de hypertension que persisteva durante plure menses e alora retornava lentemente a nivellos normotensive. Cinque menses post le operation le pression sanguinee esseva 110/70 mm Hg. In le curso de iste mesme intervallo de cinque menses, le exsudatos, hemorrhagias, e papilledema vidite in le examine fundoscopic ante le tempore del operation se resolveva completemente, e etiam le anormal constatationes in le urina dispareva. Al tempore del presente reporto-28 menses post le operation-le patiente es completemente asymptomatic e insiste que illa se senti melio que a non importa qual tempore durante le decennio ante le operation. Es describite le avantages del accesso transabdominal pro le ablation chirurgic de functionante tumores chromaffin. Le valor practic del technica de Goldenberg pro le determination de catecholamina urinari in le diagnose de functionante tumores chromaffin es sublineate.

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RESTENOSIS OF THE MITRAL VALVE*

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RESTENOSIS of the mitral valve is a new clinical entity which has been made possible by the recent advances in cardiac surgery. Its recognition is of great importance, as it may require surgical interference, in the hope of correcting the recurrent pathologic situation.

This report presents an instance of restenosis of the mitral valve, seen at autopsy, in a patient who had a good result from mitral commissurotomy and

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died three years later as a direct consequence of renewed stenosis of the mitral

Occasionally patients who have undergone mitral commissurotomy for the relief of mitral stenosis do well for variable periods of time, only to relapse and show evidence of recurrent circulatory embarrassment. This may be due to many factors, which require proper recognition prior to attempted correction.

In this discussion, only those cases are considered in which the operation was performed for uncomplicated mitral stenosis, without other valvular disease, and most particularly without significant mitral incompetence, either before or after surgery. Also not considered here are those cases in whom the actual performance of mitral commissurotomy was found to be impossible at the time of thoracotomy, but who frequently showed considerable temporary increase of their exercise tolerance after the incomplete operation. Nor are those cases included in which the surgeon felt at the time of operation that he was not able to do what is now considered to be a complete commissurotomy—separating the valve leaflets to the annulus, plus subvalvular dissection of the fused chordae

When evidence of recurrent circulatory failure presents, this may manifest itself primarily in the greater circulation, in the pulmonary cycle, or in a combination of both. If there is primarily systemic involvement, failure of the right heart or increased resistance in the pulmonary circulation is responsible. Unrecognized tricuspid stenosis, present in approximately 5% of cases of mitral stenosis, may be found, as may pulmonary arteriolosclerosis, secondary to longstanding preoperative mitral stenosis. Pulmonary emphysema, or pulmonary fibrosis or bronchial lesions, or multiple small pulmonary infarctions, may lead to pulmonary hypertension. If there is evidence of both right and left ventricular insufficiency, the possibilities include intrinsic myocardial failure and chronic rhythm disturbance, such as auricular fibrillation, of an uncontrolled nature. If the circulatory embarrassment is primarily manifested in the pulmonary circuit, the mitral valve may well be at fault, and the possibilities of mitral insufficiency or restenosis must be borne in mind. Naturally, in a system as complicated as the human body, and subjected to as many stresses as is a patient with rheumatic heart disease after cardiac surgery, a multiplicity of influences can be at play.

The problem of restenosis of the mitral valve has already been the center of some discussion and difference of opinion. Glover 1 stated unequivocally that restenosis does not occur if an adequate procedure, such as defined above, has been performed. In 50 cases in his series there was not a single instance of restenosis. He also made the very plausible argument that restenosis would be difficult in the face of the avascularity of the mitral valve leaflet. This point is underscored by others.2 Muller,3 in reporting two cases studied anatomically after commissurotomy, concluded that "healing together of the incised borders of the commissures after commissurotomy probably does not occur." These opinions, however, do not obviate the argument of those who feel that a postoperative endocardial thrombus at the site of valvular incision may be the nidus of refusion.

Others do report the occurrence of restenosis of the mitral valve as a late complication of surgery; Brock 2 described four cases that he re-operated upon out of a series of 350; Keyes & mentioned one operated case and four suspected ones out of 180 procedures, and Wood ⁵ indicated his belief that "in an extensive experience, restenosis occurred in 5%."

All authors agree on the need for a satisfactory surgical procedure, as well as an accurate appreciation of what was done at operation. This is particularly important at the time of recurrent circulatory failure. In this connection, another facet becomes more and more important, and assumes an insidious role, as its presence may at times be difficult of detection: continuous or recurrent rheumatic activity may in many cases be the cause for recurrent stenosis of the mitral valve, and may indeed be responsible for extensive nonmitral cardiac damage.

It seems plausible that the inflammatory reaction which was initially responsible for the valvular deformity may return and continue its destructive effect on the valve; it becomes even more significant when one considers the findings of Soloff et al., who found histologic stigmata of rheumatic activity in the auricles of 40.5% of operated cases. It is well known that the correlation of histologic and clinical evidence of rheumatic activity is not satisfactory, and that the discrepancy is in favor of the former; as a result, probably a much larger number of patients with smouldering rheumatic activity are operated on than can be diagnosed by our present means of clinical evaluation. Hellems resented the case of a mitral valve (studied by catheterization) which was 0.8 sq. cm. before and 2.0 sq. cm. after operation, in a patient who had had an acute episode of rheumatic fever eight months postoperatively. When the mitral valve was reexamined two years after operation it was smaller than before the procedure.

CASE REPORT

The patient was a 27 year old white man who was admitted on March 2, 1954, and died on March 12, 1954, with evidence of severe congestive heart failure and multiple pulmonary emboli.

The past history included an attack of rheumatic fever as a child, although no further details are known. In 1944 he was first informed of the presence of a heart murmur. Nevertheless, he served in the Army and was given a regular discharge in 1947. In 1948 he noted the onset of weakness and weight loss, and in 1949, following the appearance of several episodes of hemoptysis, was hospitalized with congestive failure. At that time the diagnosis of rheumatic heart disease with mitral stenosis was made, and on February 10, 1950, a mitral commissurotomy was performed by Dr. Charles P. Bailey, of Philadelphia. At the time of operation the mitral valve was reported to be "heavily calcified and rigid," and it was stated that "the tiny slit, under no condition would admit the insertion of a finger." Both the anterolateral and the posterior commissures were incised with the guillotine knife, and the surgeon reported "after that not only was it easy to insert a finger into the ventricle and move it freely about, but the valve showed considerable pliability and it was evident that a good amount of valve function had been restored." It was the impression of the surgeon that "he had some regurgitation (before commissurotomy), but that it was not considered to be of any particular significance." He felt that he had "increased the regurgitation somewhat, but that the net gain in the size of the opening would greatly

Following the operation the patient continued maintenance on digitalis but was able to do light work, and had no major difficulties until January, 1953, when abdominal pain began. In February, 1953, he underwent an appendectomy, and in August, 1953, developed full-blown congestive heart failure, with ascites, exertional

dyspnea and pedal edema. From then on, cardiac decompensation increased in severity, with the addition of hemoptysis and icterus and the onset of a febrile course. There was no history suggesting frank rheumatic activity after the operation.

On admission the physical examination showed an acutely ill white man with the following pertinent physical findings: There were generalized icterus, moderate dyspnea and ascites. Blood pressure was 90/74 mm. of Hg; ventricular rate, 112; auricular fibrillation. There was dullness over the right base, with impairment of breath sounds. Cardiac examination showed the point of maximal impulse to be 2 cm. to the left of the left midclavicular line. There was a systolic thrill at the apex, associated with a grade 3 systolic high pitched murmur, and a diastolic murmur at the apex, which was heard inconstantly because of the auricular fibrillation. The liver was enlarged six fingerbreadths below the costal margin, and there was 3 plus bilateral pedal edema.

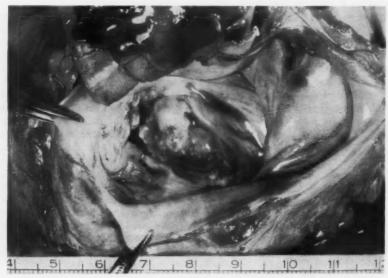


Fig. 1.

The significant laboratory findings included a leukocytosis of 14,150 and a hemoglobin of 12.5 gm. %. Blood urea nitrogen was 27 mg. %; total serum bilirubin, 13.7 mg. %; antistreptolysin titer, 250 to 300 ASL units per cubic centimeter. The electrocardiogram showed right axis deviation, auricular fibrillation and right ventricular preponderance. Chest film demonstrated the cardiac silhouette to be somewhat enlarged, with areas of radiopacity suggestive of multiple pulmonary infarctions.

At autopsy the heart (with pericardial adhesions) weighed 800 gm. and showed extensive chronic adhesive pericarditis, as well as moderate degrees of pleuropericardial adhesions. The right atrium was only slightly enlarged, having a circumference of 9 cm. The foramen ovale was closed 4nd the right auricular appendage contained a thrombus. The tricuspid valve had a circumference of 12 cm., and its leaflets were thin and delicate except for the anterior leaflet, where over an area of 3.0 by 0.5 cm. the free margin was thickened in a nodular fashion, with slight thickening of the appropriate chordae tendineae. The wall of the right ventricle measured

between 6 and 7 mm. in thickness, but there was no dilatation of the right ventricular chamber. The pulmonic valve had a circumference of 9 cm. and was thin and delicate. The ascending portion of the pulmonary artery contained a number of atheromatous plaques. The left atrium had a circumference of 15 cm. and was dilated, and the left auricular appendage was surgically absent. The mitral valve in the closed state (figure 1) was calcified, firm, nonelastic and nonmovable, and the lumen of the mitral valve measured 2.5 cm. by 0.3 to 0.35 cm. The examiner's finger could not be passed through the orifice. In the opened state (figure 2) the valve had a circumference of 8 cm., and the leaflets were contracted and composed of calcified nodules. There was no evidence of bacterial endocarditis, nor could the commissurotomy lines be detected. The chordae tendineae were fused and thickneed. The wall of the left ventricle measured between 13 and 15 mm. in thickness, and the ventricular chamber was not



Fig. 2.

dilated. The aortic valve had a circumference of 7 cm., and the leaflets were fused at their aortic attachments for a distance of 0.5 mm., with their free margins showing minimal rounded thickening, never measuring more than 0.5 mm. in diameter.

The remainder of the autopsy showed multiple pulmonary infarctions, both recent and old, chronic passive congestion of all viscera, ascites, bilateral pleural effusion, focal fibrosis of the myocardium, atherosclerosis of the pulmonary arteries, cardiac cirrhosis, old encephalomalacia of the left caudate nucleus, and early bronchopneumonia of the right lower lobe.

Microscopic examination of multiple sections of the myocardium and mitral valve showed focal areas of frequently perivascular myocardial fibrosis. These may well represent sites of previous rheumatic inflammation. No Aschoff bodies could be demonstrated in these zones. Sections of the mitral valve showed diffuse hyaline thickening of the valve leaflet, with calcific replacement of the inner zones. The hyaline connective tissue, which on elastica van Gieson's stain contained a moderate number of elastic fibers, merged directly with the zones of calcium in this area. In

some areas narrow lines of calcium continued along the otherwise normal endocardium. In other areas large foci occupied and widened the base and leaflet of the mitral valve. The central aspects of these areas were composed of calcium, surrounded by zones composed of dense hyaline connective tissue and dense collections of lipoid-laden histiocytes. These strongly resembled similar cells seen in the base of atheromatous plaques. Occasional zones of amorphous material were present here. Beyond this were occasional irregular zones of granulation tissue, composed predominantly of collagen fibrils, occasional fibroblasts, histiocytes and many capillaries filled with blood. In this area there was a moderate number of small arteries, the walls of which were concentrically and greatly thickened by an intimal increase of moderately dense connective tissue. Elastica van Gieson's stain confirmed this intimal thickening, and showed further that the internal elastic lamina was prominent and reduplicated. Beyond these zones was intact myocardium. Of interest was the presence of a moderate degree of atherosclerosis of the main left coronary artery. There was no evidence in the valve or its base of brown granular pigment-laden histiocytes in any of the sections, suggesting phagocytosis of blood pigment, or of Aschoff bodies.

DISCUSSION

In summary, the case is one of a 28 year old white man with rheumatic heart disease and mitral stenosis who underwent what appeared to have been an adequate mitral commissurotomy two and one-half years before the recurrence of congestive heart failure and three years before death. The significant observation was the fact that the mitral valve, which was freely movable and admitted the surgeon's finger at operation, was completely rigid and calcified at autopsy, and had a lumen of 0.75 sq. cm., with no anatomic evidence of the previous commissurotomy.

It is believed that the dynamic obstruction at the mitral valve was in essence responsible for the greater share of the patient's deterioration, the pulmonary congestion setting the stage for failure of the right heart and multiple pulmonary thrombo-emboli, with subsequent peripheral passive congestion. The tricuspid and aortic valves, to be sure, were involved in a rheumatic process, but this was not of a magnitude to be considered significant. In the former only a relatively small focal area of the anterior leaflet was slightly thickened, and in the latter the fusion of the cusps was minimal, and comparable to that frequently found at autopsy in patients with no clinical evidence of heart disease.

There is no definitive explanation for the obvious restenosis of the mitral valve in this case, although several attractive theories may be offered. Reactivation of the rheumatic state is always a likely possibility in a patient who has previously been affected by it; it is well known that these patients are more susceptible to rheumatic activity than is the rest of the population, and that its recognition is difficult clinically.

Although there was no overt episode between operation and return of congestive failure, this does not rule it out, and the abdominal pain in January, 1953, culminating in an appendectomy one month later, may have been the abdominal equivalent of this condition. There was no histologic evidence of recent rheumatic activity, either in the myocardium or in the region of the fibrotic and calcified valve. The absence of such findings appears to be of some importance. The second mechanism, whereby restenosis may take place, is the organization and calcification of a postoperative endocardial thrombus. As mentioned above,

this theory has much in its favor, and obviates the criticism that the avascular fibrotic valve leaflet cannot form de novo granulation tissue. However, in our case this appears unlikely, as there was no histologic evidence of organized thrombus. The complete absence of hemosiderin-laden histiocytes and lack of superficial granulation tissue point to this. Another possible explanation, however, is opened by the findings in this case: the presence of extensive zones of lipid-laden histiocytes, strongly resembling the process seen in atheromatous plaques in the abdominal aorta, suggests a comparable situation. In the terminal portion of the aorta the increased intravascular eddy currents are responsible for the formation of atheromata completely out of proportion to those seen elsewhere in the same circulatory system. Here lipid material is laid down, to be surrounded by granulation tissue which is later converted into hyaline connective tissue. It may also become necrotic and subsequently be calcified. It is possible that the mitral valve, which is subject to excessive hemodynamic stresses and strains, particularly after operation, reacts in a similar fashion: lipid is laid down and some of it becomes hyalinized; the remainder first undergoes necrosis, and then calcium is deposited.

As a result of these changes, recontraction of the leaflet, and particularly the annulus, takes place, and the stage is set for restenosis. It is of interest that much of the latter change described was found at the base of the leaflet, in the

region of the annulus.

Despite the uncertain etiology of this phenomenon, a high index of suspicion is needed so that this specific defect may be corrected.

SUMMARY

A case is presented of restenosis of the mitral valve, seen at autopsy three years after successful mitral commissurotomy. Possible etiology and implications are discussed.

ACKNOWLEDGMENT

Acknowledgment is made to the Medical Illustration Department of the Veterans Administration Hospital, East Orange, New Jersey, for the photographs.

SUMMARIO IN INTERLINGUA

Un del complicationes de apparition recente in commissurotomia del valvula mitral es le problema del re-stenosis. Isto es specialmente ver in le casos de patientes operate a bon successo pro stenosis mitral qui postea progrede ben durante varie periodos de tempore. Quando tal patientes disveloppa recurrente signos de embarasso circulatori, le tableau clinic a ille tempore debe esser differentiate ab disfallimento myocardial (super le base del accompaniante insufficientia myocardial), ab active infection rheumatic, ab morbo tricuspide, e ab hypertension pulmonar.

Il existe un certe divergentia in le opiniones in re le occurrentia de re-stenosis del valvula mitral. Un numero del theorias avantiate con respecto a su etiologia es discutite. Recurrente activitate rheumatic e organisation de un thrombo endocardial al sito del commissurotomia es considerate prominentemente. In plus le autores mentiona le possibilitate de un processo analoge al formation de un placa atheromatose al sito del augmentate currente de Foucault intravascular.

Es presentate le caso de un masculo blanc de 27 annos de etate qui moriva tres annos post le effectuation a bon successo de un commissurotomia pro stenosis mitral,

sequite initialmente per bon resultatos therapeutic sed subsequentemente un recurrente discompensation circulatori. Al necropsia le valvula mitral (le operation del qual habeva essite adequate) exhibiva un restringite orificio calcificate.

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SPLENIC RUPTURE IN INFECTIOUS MONONUCLEOSIS*

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SINCE splenic rupture is a rare complication of mononucleosis, knowledge of the incidence of this complication is gained only as cases are reported. Details of the clinical course of patients with ruptured spleen are often lacking because many cases have been recorded by pathologists, who are unlikely to have personal knowledge of such details.

Review of the two cases to be described, and also of some published case reports, suggested that early manifestations of splenic rupture were unrecognized. In one instance 1 a patient hospitalized with a diagnosis of mononucleosis later went into shock and died of a ruptured spleen, yet the antemortem diagnosis of splenic rupture was "hardly entertained." Patients with infectious mononucleosis and early splenic rupture may have symptoms pointing toward this complication hours or days before the most serious intra-abdominal bleeding occurs.2 On the other hand, as in Stobbe's case,3 the first symptom of splenic rupture may be followed by death in 20 minutes. The life-saving importance of early diagnosis is obvious.

Knowledge of the clinical picture of uncomplicated mononucleosis will enable physicians to understand the significance of unusual features which may indicate the onset of splenic rupture. A clearer understanding of the clinical aspects of uncomplicated infectious mononucleosis begins when the adjective "protean," found in almost every description of this disease, is discarded. This basic

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approach is not academic. It is of fundamental importance for the early diagnosis of splenic rupture and other complications. If mononucleosis is regarded as protean, the inexperienced observer is led to believe that almost any symptom or sign can be dismissed as an oddity to be expected in a disease notoriously changeable. However, when it is realized that the clinical picture of uncomplicated mononucleosis is fairly consistent,^{4, 5} the occurrence of an unusual clinical manifestation is more likely to lead to early recognition of a complication.

The constancy of the clinical picture of uncomplicated mononucleosis, when diagnosis is based on hematologic and serologic confirmation, has been emphasized in other writings.^{6, 7} It need only be emphasized here that severe abdominal pain is rarely seen in uncomplicated mononucleosis. Even moderate abdominal pain is rarely encountered. In a series of 81 personally observed patients,⁷ only one had abdominal pain, and it was only mild. In a series of 153 personally observed patients whose clinical histories were carefully recorded, the senior author has seen only two with severe abdominal pain. One of these had a ruptured spleen, and is reported as case 1 herein; the other patient was operated on, but the spleen was found to be intact.

CASE REPORTS

Case 1. This patient, a 23 year old unmarried white male, experienced general malaise and mild headache on November 16, 1954. On November 23, 1954, his temperature was recorded as 100° F. Increase in intensity of symptoms led to hospitalization on November 26, 1954. No abdominal or chest pain had been present.

Physical examination on admission disclosed a mild inflammation of the pharynx with a little exudate. About 30 red petechiae, each about 1 mm. in diameter, were symmetrically distributed on the soft palate. Posterior cervical, axillary and inguinal lymph nodes were moderately enlarged; the anterior cervical lymph nodes were greatly enlarged and slightly tender. Temperature was 101° F.; pulse rate was 84/min. The ward physician made a clinical diagnosis of mononucleosis. On November 27, 1954, the leukocyte count was 8,600, with 70% lymphocytes. Almost all lymphocytes were atypical. Hemoglobin was 13.1 gm. %, and hematocrit was 43%. Sedimentation rate was 37 mm./hr. On this day, the twelfth day of illness, the heterophil antibody reaction was positive in a titer of 1:112, and in a titer of 1:56 after absorption with guinea pig kidney. Serum bilirubin on November 27, 1954, was 0.4 mg. and cephalin flocculation was 3 plus. Electrocardiogram was normal. Roentgenography of the spleen (routine on all mononucleosis suspects) on November 26, 1954, disclosed slight enlargement. Two days later roentgenography showed increased enlargement of the spleen.

On the day after admission, lymph node enlargement and pharyngeal inflammation of the throat increased. The patient's temperature remained about 101° F. During the night of November 27/28, 1954, he vomited and had three loose defecations. He felt faint when he arose from the toilet seat after defecating, but did not fall. On November 28 his spleen was palpable, and the ward officer found the abdomen to be diffusely, although only slightly, tender, but not distended. During the evening of November 28, pulse rate rose to 96/min., although the temperature peak was still only 101° F. During the night of November 28/29 he had increasing abdominal pain, mainly in the left hypochondrium, which radiated up to the left chest and to the left shoulder area. The pain in the left chest worsened when he breathed deeply or tried to cough. His pulse rate ascended to 112/min.; he was very apprehensive. He was seen by the physician on night call, who found moderate, generalized abdominal tender-

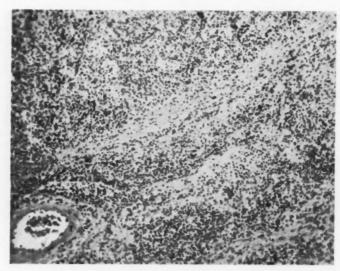


Fig. 1. Low power showing infiltration of splenic trabecula with mononuclear cells.

ness and muscle spasm on the left side of the abdomen. He considered the possibility of a ruptured spleen, but after consulting textbooks and reading that patients with mononucleosis could present almost any symptom and that abdominal pain was "not uncommon," his suspicion of splenic rupture was dispelled. On the morning of November 29 the patient was seen by the senior author. Pain in the left hypochondrium

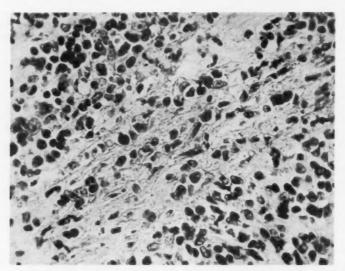


Fig. 2. High power showing infiltration of splenic trabecula with mononuclear cells.

was severe. Examination disclosed slight bulging of both flanks, with shifting dullness. Intestinal sounds were absent. Moderate generalized abdominal tenderness and moderate muscle spasm were elicited. Pulse rate was 106/min. Blood pressure was 120/60 mm. Hg. The bedside diagnosis of splenic rupture was made and was confirmed by the report of blood studies ordered at once. Hemoglobin had dropped to 9.9 gm. % and hematocrit had dropped to 33%.

An emergency abdominal operation during the morning of November 29 disclosed a large subcapsular hematoma of the spleen and approximately 1,200 c.c. of free blood in the peritoneal cavity. The spleen was removed without incident. Recovery was uneventful. His temperature and pulse rate gradually declined after the evening of operation and reached normal levels on December 6. Gross examination by the pathologist revealed a large subcapsular hematoma and an irregular laceration of the inferior surface of the spleen. Microscopic examination revealed that the

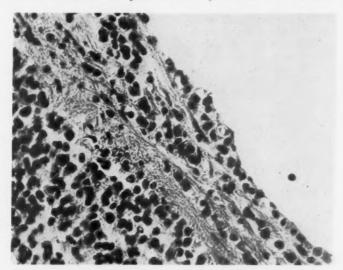


Fig. 3. High power showing infiltration of splenic capsule with mononuclear cells.

capsule was infiltrated with mononuclear cells, most of which appeared to be lymphocytes. The general architecture was normal. The malpighian bodies were somewhat smaller than usual. There was some increased cellularity of the red pulp, although the sinuses were fairly prominent. The sinuses contained an excessive number of nucleated cells, most of which appeared to be large mononuclear cells. There was a-striking change in the trabeculae, characterized by infiltration with lymphocytes. In some areas the trabeculae appeared largely replaced by infiltrate. Some of the veins showed subintimal infiltration with large mononuclear cells which apparently represented atypical lymphocytes.

Case 2.* This 25 year old male was hospitalized on September 28, 1953, be-

^{*} This patient was seen only by the junior author, who had intended to publish a separate case report but died suddenly before he could do so. However, he had requested advice from the senior author concerning this case and later sent him a final summary, which appears below. It seemed proper that his case report be included in this paper, particularly since it too illustrates that mononucleosis patients with severe abdominal pain, especially with radiation to the left shoulder, may have splenic rupture and must be watched carefully, if timely operation is to be performed.

cause of left upper quadrant pain of four days' duration. Two days before admission the pain radiated upward to the left shoulder and became severe. It was aggravated by deep breathing.

On admission the pharynx was moderately inflamed. There was a decrease of intensity of breath sounds in the lower third of the left chest, with slight dullness on percussion. Palpation revealed tenderness of the left upper quadrant. Temperature was 99.6° F.; pulse rate, 84/min.; blood pressure, 140/88 mm. Hg. Blood count on admission revealed a total leukocyte count of 9,000, with 63% lymphocytes, 19 of which were atypical. Hemoglobin was 13.6 gm. % and hematocrit was 40%. A clinical diagnosis of mononucleosis was made. On the day after admission the heterophil antibody titer was 1:112. This titer rose to 1:448 on October 5 and then gradually declined. (Guinea pig kidney absorption tests were not reported.)

On the day after admission the spleen was palpable. Roentgenography disclosed evidence of a pleuritic or pneumonic reaction at the left cardiophrenic angle. On October 4 the abdominal pain, which had partially subsided, became worse. Examination revealed only abdominal distention. On October 5 abdominal pain increased and radiated into the left chest and left shoulder. Walking to the toilet caused great fatigue. Nevertheless, the diagnosis of splenic rupture was not entertained until the next day, when it was apparent that his mucous membranes were excessively pale. His abdomen was abnormally rounded; shifting dullness was present. Hemoglobin on this day was 5.7 gm. %, with a hematocrit of 18%. An emergency splenectomy was performed. When the peritoneal cavity was incised a cascade of dark red blood gushed out under pressure. The volume of blood was estimated at about 3,000 c.c. The spleen was about three times normal size, soft and friable. A rent was found in the capsular area near the inferior pole of the spleen, on the posterior aspect. The postoperative course was not remarkable.

COMMENT

When splenic rupture occurs in a patient known to have infectious mononucleosis, this complication should be diagnosed readily. Yet review of both of the cases described above, and of other case reports, indicated that the diagnosis was not made as promptly as possible. An important cause of delay is the perpetuation of the erroneous, but regularly repeated, statement that mononucleosis is a "protean" disease. However, the clinical picture of uncomplicated mononucleosis is fairly uniform. It has been described in detail elsewhere; two basic syndromes—the pharyngeal and the typhoidal—were described.

After a diagnosis of mononucleosis has been made, the complication of splenic rupture, with its typical clinical manifestations, should be readily recognized. In our experience, and in the experience of Bernstein and others, severe abdominal pain is rare in mononucleosis. This is at variance with statements perpetuated in some textbooks: that abdominal pain secondary to enlarged mesenteric lymph nodes is not uncommon, and that acute appendicitis may be simulated. History, physical examination and hematology enable a physician to differentiate between uncomplicated mononucleosis and acute appendicitis, if he understands the signs and symptoms of these diseases. The physician on night call who examined our first patient considered splenic rupture, but his clinical acumen was blunted when he consulted a textbook and read that abdominal pain was not uncommon in infectious mononucleosis.

When a patient with mononucleosis has severe, or even moderate, pain below

the left costal margin, one should immediately think of the possibility of a ruptured spleen, especially if the pain is preceded or followed by sudden faintness or weakness. Usually the pain radiates to the left shoulder area, especially when the patient is lying down. It may be caused to radiate by raising the foot of the bed from 10 to 20 minutes. The pain may be accompanied by indications of peritoneal irritation, such as one or more emeses, a few semisolid defecations, abdominal tenderness and, later, distention. Muscle spasm or rigidity will be found sooner or later; and after there has been enough bleeding, shifting dullness may be observed. By the time low hematocrit and low hemoglobin levels are found, the diagnosis is self-evident. An extremely valuable clue is the pulse rate, which is almost always under 100/min. in patients with uncomplicated mononucleosis. When a patient with mononucleosis has severe left abdominal pain and an increasing pulse rate, the probability of splenic rupture is great. (This sign was present in case 1.)

Although pain in the left upper abdominal quadrant usually precedes the easily recognizable signs of hemorrhage, sometimes by as long as two or more days (illustrated in case 2), Ziegler and Stobbe each reported a fatal case in which abdominal pain was not mentioned. Ziegler's patient felt weak at 10:30 a.m., went into shock at 11:40 a.m., and died at 1:30 p.m. Knowledge of the clinical clues indicating splenic rupture must be accompanied by awareness of the necessity for fast action if lives are to be saved. Patients can die very rapidly, as is illustrated by the case reported by Stobbe. His patient, a 19 year old male, died 20 minutes after suddenly feeling very weak. However, patients may bleed only a little from a rent in the splenic capsule before a blood clot temporarily causes bleeding to stop. Several such episodes may take place and may be followed by temporary improvement. However, at any moment massive, fatal bleeding may commence. Therefore, when a mononucleosis patient has several left upper abdominal or left subcostal pains and physical examination reveals evidence of peritoneal irritation and an increasing pulse rate, it is better to explore surgically than to wait for hematologic proof of hemorrhage, for this clinching evidence may be obtained too late to save the patient.

It is doubtful whether splenic rupture of hospitalized patients can be prevented. Excessive palpation of the spleen by medical students and interns has been deemed unwise, but a causal relation between palpation and rupture is hard to prove. It is unlikely that splenic rupture occurs more frequently in teaching hospitals than in others. Our two patients were not palpated excessively. Spleens may rupture while patients are defecating, or while lying in or twisting about in bed, or engaging in routine activities which are unassociated with hard labor.

Spleens which rupture show remarkable lesions. There is such striking dilution of the fibromuscular structure of trabeculae and capsule by mononuclear infiltrate, with complete replacement in areas, that a tear seems to be inevitable, regardless of limitation of physical activity. Inasmuch as rupture of the spleen usually occurs in the first three weeks of illness, one can be liberal in allowing activities four weeks after onset of illness, if the patient appears to have recovered. We saw almost 200 cadets with infectious mononucleosis during six years at West Point, and started them on carefully graded reconditioning exercises about a week after they became afebrile. They returned to vigorous cadet life after

about three weeks of graduated reconditioning. None of these cadet patients had splenic rupture.

SUMMARY

1. Two cases of mononucleosis with complicating splenic rupture are reported. Both patients were operated on successfully.

2. The clinical picture of *uncomplicated* mononucleosis is not protean. When unusual clinical manifestations are found, a complication should be suspected.

3. Severe abdominal pain is rare in mononucleosis. When severe or even moderate abdominal pain is complained of, splenic rupture should be considered. Radiation of pain to the left chest and shoulder and an increasing pulse rate strengthen the probability of a ruptured spleen.

4. If a patient with mononucleosis goes into shock, with or without abdominal

pain, splenic rupture may be the cause.

5. Prompt operation is of vital importance. Therefore, it is better to explore if the diagnosis is probable, even if the blood count has not yet reflected hemorrhage, than to wait for convincing hematologic proof of hemorrhage.

ACKNOWLEDGMENTS

We are indebted to Dr. Robert T. McCluskey, of the Department of Pathology, Bellevue Hospital, New York, N. Y., for interpretation of histopathology and microphotography. We wish to acknowledge the great help of Dr. Robert W. Wright, who operated on the first patient, and Dr. Nicholas De Vito, who operated on the second patient.

SUMMARIO IN INTERLINGUA

Ruptura splenic—un complication rar de mononucleosis—es usualmente reportate per pathologos, de maniera que pauc information de interesse clinic se trova detaliate in le litteratura.

Il es del prime importantia que non-complicate mononucleosis es reguardate como un morbo de apparentia clinic satis constante: Illo non es un morbo proteic. Sever dolores abdominal se manifesta rarmente in mononucleosis complicate. Quando illo occurre (specialmente quando illo occurre in le quadrante supero-sinistre del abdomine), ruptura splenic debe esser suspicite. Proque patientes con mononucleosis non-complicate ha usualmente un relative bradycardia, le presentia associate de un acceleration del pulso con crescente severitate del dolores abdominal reinfortia le suspicion de ruptura splenic. Radiation del dolor al spatula sinistre—un signo importante—es frequentemente producibile per elevar le pede del lecto.

Ruptura splenic pote occurrer in un serie de episodios, separate per intervallos de transitori melioration partial. Evidentemente, in le curso del tempore obvie signos de peritonitis e de acute anemia se presenta insimul con le usual alternationes del valores hematologic. Tamen, si le objectivo es salvar un plus grande numero de patientes, il es desirabile establir le diagnose ante que illo es grossiermente obvie.

Il es dubitose si ruptura splenic pote esser prevenite per limitar le palpation abdominal in patientes con mononucleosis. Frequentemente le splen se rumpe quando le patiente defeca, se contorque in le lecto, o executa altere activitates trivial. De facto, examines microscopic de splenes rumpite revela talmente frappante grados de dilution del structura fibromuscular del trabeculas e del capsula per infiltratos mononuclear (con reimplaciamento total in certe areas) que un ruptura pare inevitabile si o non le activitate physic es restringite.

Proque rupturas del splen occurre usualmente durante le prime tres septimanas del morbo, il es possibile permitter grados plus liberal de activitate a partir de quatro septimanas post le declaration, providite que le patiente manifesta provas de restablimento. In le curso de sex annos nos ha vidite quasi 200 cadettos de West Point con mononucleosis infectiose e initiava les a cautemente gradate exercitios de reconditionamento circa un septimana post que illes deveniva afebril. Post circa tres septimanas de iste gradate reconditionamento illes retornava al vita rigorose del cadettos. Nulle de illes habeva ruptura splenic.

Es reportate duo casos, con superviventia post operation.

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ISCHEMIC NECROSIS OF THE ANTERIOR TIBIAL MUSCLE: CASE REPORT WITH AUTOPSY FINDINGS, AND REVIEW OF THE LITERATURE*

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Acute ischemic necrosis of the anterior tibial muscle is rarely observed. Necrosis associated with vigorous exercise, indirect injury, transfusions or systemic illness has been recognized, but only a few such cases have been reported. Because of the confusing clinical picture and because prompt recognition is necessary to prevent or minimize prolonged disability, the following additional case is described. The literature is reviewed with especial attention to certain clinical features of the syndrome.

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CASE REPORT

The patient, a 46 year old white male, was admitted to the Veterans Administration Hospital, Northampton, Massachusetts, on May 6, 1952, for treatment of a schizophrenic reaction, paranoid type. Except that he had required psychiatric treatment for 15 years, his medical history was negative. Physical and neurologic examinations on admission were not remarkable.

His hospital course was uneventful until the final illness. He received electroshock in early 1953. Reserpine was begun on July 2, 1954, with a dose of 0.25 mg, three times a day. He was withdrawn and seclusive. His only physical exertion consisted of short walks to meals and mild corrective exercises.

On the morning of February 7, 1955, he had a grand mal seizure. Because of his mental agitation, no reliable history could be obtained. He was transferred immediately to the Medical Service.

Physical examination revealed bilateral basal râles. There were occasional ventricular premature contractions. An aortic systolic murmur of moderate intensity was heard. The right dorsalis pedis pulse was considerably stronger than the left. The calves were hypertrophied but were not tender. There were questionable petechiae on both shoulders. The temperature (rectal) was 100.8° F.; pulse, 82; respirations, 24 per minute; blood pressure, 148/88 mm. of Hg. An electrocardiogram, skull x-ray and chest x-ray were normal.

On the following day the patient vomited twice. His urine was dark brown, negative for bile but strongly positive for occult blood. There was albuminuria (2 plus) and microscopic hematuria (25 to 30 red cells per high power field). The white blood cell count was 13,200, with 82% polymorphonuclear forms, 17% lymphocytes and 1% eosinophils.

On February 10, three days after the onset of his illness, a red, warm and indurated area was discovered on the anterior aspect of the left leg. This was considered a cellulitis and treated with warm compresses and procaine penicillin G. No pattern of diagnostic significance was noted on an electro-encephalogram taken that day.

On the following day the area on the left leg was brilliant but blanched on pressure. Erythromycin was started.

On February 14, seven days after the onset of the illness, a left foot drop was present. A surgical consultant found prominent anterior compartment muscles and an indentation at the upper end of the compartment. On February 15 incision and drainage of the left leg were attempted (Dr. D. R. Hayes). Through a three inch incision the muscle was examined. There was no resistance on palpation. A smear from the leg, cultured under both aerobic and anaerobic conditions, grew nothing. A fragment of muscle tissue, removed at the time, was necrotic and acutely inflamed (figure 1). One minute artery contained a recent thrombus.

Orthopedic measures controlled the foot drop. Micrococcus (Staphylococcus) pyogenes, var. albus, was cultured from blood drawn on February 18 and again on February 24, but a blood culture of February 28 grew nothing.

On February 22 the patient's temperature began to rise. Penicillin and erythromycin, discontinued on February 21, were resumed on February 24.

By February 28 the patient's condition had become much worse. His temperature remained elevated. He appeared to have a fine macular rash on the left shoulder and neck. Although there were coarse rhonchi in the chest, a chest x-ray on that date showed no significant abnormalities. The clinical impression was bacteremia.

Physical examination on March 1 was unchanged. The dose of crystalline penicillin was increased, and streptomycin was substituted for the erythromycin, which the patient refused to take.

Oxygen was started on March 3. On the following day the doses of penicillin and streptomycin were increased, and chloramphenicol by the intramuscular route was added. In spite of all supportive and antibiotic treatment, the patient died at 5:57 a.m. on March 5, 1955.

Radiographs of the left leg on February 16 and March 3 showed no bony changes. The white cell count remained elevated. On March 1 there were 17,400 white cells, with 84% polymorphonuclear forms. Serial urine specimens contained small numbers of red cells. A nonprotein nitrogen determination on March 1 was 71 mg. per 100 ml.

The management of this patient was complicated by a psychosis. Evaluation of muscle function was not possible. Electromyographic studies were not done.

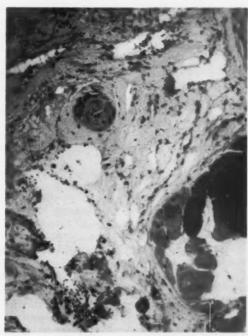


Fig. 1. This photomicrograph of material obtained at the time of exploration shows normal and necrotic (dark) muscle (right center), inflammatory cells (top).

The autopsy was performed by Dr. William J. Welch and Dr. William Kaufmann. Significant changes were confined to the lungs and the left leg. Acute congestion and an acute, patchy, bronchial and lobular pneumonia were present in the lungs. There were massive emboli in the pulmonary arteries.

The edges of the surgical incision in the left leg were slightly eroded and the surrounding tissues were indurated. On finger exploration through a lengthened incision only necrotic and ischemic muscle was present. There were no evidences of infection, nor were any foreign bodies found. Microscopic examination confirmed the presence of necrosis. There were no autopsy findings to explain the positive blood cultures, nor were there any neuropathologic changes to explain the convulsive seizure at the onset of the illness.

REVIEW OF THE LITERATURE

The development of anterior tibial necrosis following exercise was described by Vogt¹ and Severin² in 1943. Additional papers³-10 have brought to 20 the number of cases following exercise, indirect injury, blood transfusion or systemic illness. Although the total number of published reports is small, the condition may not be rare. Pretibial pain has been recognized in patients who did not subsequently develop a disabling necrosis. 6,8 The pathology is similar to or identical with that of Volkmann's ischemic contracture, and undoubtedly there have been instances of confusion in diagnosis. C. E. Horn⁴ has suggested that idiopathic clawfoot may follow insufficiency of the anterior tibial artery, producing an ischemic contracture of the anterior tibial muscle and long extensor muscles of the toes. The acute illness in these patients may have been overlooked or forgotten.

In an examination of the literature, attention has been directed to the clinical and pathologic features of the condition. The occurrence, prodromal symptoms and precipitating events, clinical picture and differential diagnosis, pathogenesis and pathology, treatment and outcome are reviewed.

The development of ischemic necrosis following fractures and direct muscular or vascular injury will not be discussed. The following information is based on the reports of 20 patients in whom the necrosis developed without preceding direct injury.

OCCURRENCE

To date, anterior tibial necrosis without prior direct trauma has been observed only in relatively young males. The patient whose case history is presented here was 46 years old, slightly older than the 18 to 40 year range of patients previously reported. Age distribution and absence of necrosis in women may be purely chance phenomena. The precipitating events are limited neither to a specific age group nor to the male sex.

The right extremity alone was involved in 12 of the 20 cases. (In two of these cases transfusions had been given into the right lower extremity.) The left leg alone was involved in five patients, and both legs in three patients.

PRODROMAL SYMPTOMS AND PRECIPITATING EVENTS

Prodromal symptoms were mentioned in four of the 20 patients. Two patients had histories of pain in the legs following severe exertion. One patient had noticed easy fatigue of the legs for one year before the development of acute symptoms. One patient described vague pains over the anterolateral aspects of both lower limbs for nine months before the onset of the necrosis.

The syndrome followed football in seven instances, prolonged marching in two, and walking or hiking in three. Two patients in the series of Carter, Richards and Zachary 8 received transfusions into the right lower extremities; both developed anterior tibial ischemic necrosis on the right. In four patients the necrosis was precipitated by moderate or strenuous exercise, not otherwise described. One patient twisted his ankle on alighting from a train. One patient had a medical illness, possibly a rheumatic infection.

CLINICAL FINDINGS AND DIFFERENTIAL DIAGNOSIS

Ischemia of the anterior tibial muscle is usually sudden in onset. Within hours of exercise or other precipitating event there is severe pain in the anterior portion of the leg. This is followed by the rapid development of swelling, most marked over the anterior fascial compartment. The skin over the involved muscle becomes erythematous and glossy. Foot drop follows. As the process becomes chronic, the muscle may become abnormally hard on palpation.

In the differential diagnosis, at least 27 separate diseases or injuries have been mentioned. The most common erroneous diagnoses are cellulitis, phlebitis, thromboangiitis obliterans, myositis associated with bacterial or parasitic infections, acute osteomyelitis, pretibial fever and acute tenosynovitis. The evolution of the typical clinical picture and the absence of signs and symptoms associated with the confusing diseases usually suffice to establish the true diagnosis. An early and accurate diagnosis is necessary if there is to be any hope of arresting the process before irreversible changes have occurred.

PATHOGENESIS AND PATHOLOGY

What are the factors in the production of this syndrome? They can be understood better if one remembers that the anterior tibial compartment, containing the anterior tibial muscle, the extensor digitorum longus and extensor hallucis longus muscles, blood vessels and nerves, is a tight but not completely closed compartment. The opening at the lower end, however, may not be sufficient to cope with changes occurring in the compartment.

A small percentage of the cases may follow thrombosis or embolism occurring during systemic illness. In this group is included Hughes's ⁷ patient, who developed a bilateral ischemic necrosis during a medical illness, possibly a rheumatic infection. The patient described in this paper may belong in this group. A minute thrombus was found in the specimen of muscle removed at the time of exploration, and at autopsy there was massive embolism of the pulmonary arteries.

Arterial spasm is considered by some to be an important factor in the development of the syndrome. Spasm of the large arteries of the lower extremity can occur, and has been demonstrated by Sirbu and his co-workers ⁸ in patients who were explored operatively following injury. Hughes, ⁷ whose case reports were accompanied by original investigation on the vascular patterns in the lower extremities, believes that spasm may involve a large segment of the anterior tibial artery, just below the origin of the anterior tibial recurrent branch.

The role of chemical changes is uncertain. Chemical and pH alterations are known to occur in fatigued muscles, and Hughes ⁷ wondered if these changes might initiate the spasm mentioned in the preceding paragraph.

Another important factor in the development of the syndrome is increased tension within the anterior tibial compartment. Prolonged activity, which often precedes the onset of necrosis, may increase the weight of muscle as much as 20%, principally by the retention of excess fluid. The increase in volume may then aggravate an already embarrassed circulation. Carter and co-workers, in discussing the two post-transfusion patients who developed the syndrome, mentioned as perhaps significant the extravasation of blood into the anterior tibial compartment and the deleterious effects of tight bandaging on venous return through

superficial veins. Pearson, Adams and Denny-Brown ⁶ suggested in their report that violent muscular contraction may have led to rupture of muscle fibers and hemorrhage and an increase in muscle volume.

Whether actual changes occur in the vessels themselves is not known. C. E. Horn 4 demonstrated marked thickening of all layers of the arteries involved in the ischemia. Hughes 7 did not agree with the theory of hypertrophy and fibrosis of the anterior tibial artery as a result of repeated demands of muscle during strenuous exercise.

Although there may be disagreement on pathogenesis, there is agreement on pathologic changes. Ischemic necrosis is present. In spite of the external appearance of the involved extremities, infection is not ordinarily a factor; it may be introduced at the time of surgical exploration, if extreme care is not taken. The muscle, initially soft and necrotic, becomes gray, firm and avascular. Some muscle regeneration does occur, although the ischemia prevents phagocytosis; regeneration is much slower than that observed in experiments with rabbit muscle because of the enormous bulk of human muscle. Regenerated muscle is clinically weaker than its uninjured predecessor.¹¹

Although attention has been focused principally on changes in the anterior tibial muscle, the smaller extensor digitorum longus and extensor hallucis longus do not escape damage. Evidence of changes in one or both is described in 11 of the 20 reports. A supplemental blood supply from perforating arteries may account for the less severe involvement of the extensor digitorum longus and extensor hallucis longus muscles.⁷ A complete evaluation of muscle function should be done whenever possible to determine the extent of damage within the anterior tibial compartment.

TREATMENT

The treatment of anterior tibial ischemic necrosis is divided into preventive, early and late.

As the onset of the condition is often associated with exercise, physical conditioning is an important preventive measure. Carter and his group ⁸ have emphasized that reports of the anterior tibial syndrome are lacking in trained and professional athletes, and that persons developing the condition have had an almost complete absence of preceding graduated exercise. It is reasonable to believe that a program of systematic physical training or, in the military service, a progressive series of marches, will reduce the likelihood that this disabling sequela of strenuous leg exercise will develop. There is still time for preventive measures after the onset of pretibial pain. Although many athletes "walk off" the discomfort, the use of bed-rest, elevation of the extremity, analgesics and warm applications may be preferable.

Transfusions or other intravenous therapy in the veins of the leg should be observed carefully to prevent extravasation and increased pressure in the anterior compartment. Return venous flow should not be hindered.

When there is definite evidence of muscle swelling, bed-rest is mandatory. Relief of arterial spasm is a debatable subject because of the uncertain role of spasm in the production of the necrosis. Nitroglycerin has been used. The lumbar sympathetic block is more effective, but even this may not work; Sirbu, Murphy and White 3 noted in their paper that the possibility of a distal reflex

arc, not involving the sympathetic ganglia, has been advanced by several workers. If there is no relief from a lumbar sympathectomy, periarterial sympathectomy or even arteriectomy may be necessary. Arteriectomy as a means of promoting collateral circulation was popularized by Leriche, and is based on the theory that a constricted artery, with no blood flowing through it but with sympathetic fibers still present in the adventitia, is, in fact, no artery at all but an abnormal sympathetic nerve.

Fasciotomy has been advocated for the relief of pressure. If foot drop has occurred, the stage of expected recovery with conservative measures has passed. Fasciotomy, if considered, should be done early, and is probably contraindicated once the muscles become necrotic.

Late treatment consists largely of physical therapy and corrective measures. Whirlpool, electrical stimulation, and active and passive exercise have been valuable under certain circumstances. Carter and co-authors ⁸ have remarked that it is probably useless to persevere with physiotherapy if the muscles feel hard, do not respond to stimulation, or are silent on electromyography or ischemic on biopsy. Braces and supports have a definite place in both early and late treatment. Eventual excision of the hardened and avascular muscle has been necessary in several instances. In selected cases tendon transplant may be of value; Tillotson and Coventry ⁹ passed the peroneus longus tendon subcutaneously and attached it to the middle cuneiform bone.

Unless there is definite evidence of infection, antibiotics are of questionable value. They are usually given when the diagnosis is uncertain or when the process is considered inflammatory. If there is no surgical interference, there is little likelihood of wound contamination.

OUTCOME

Of the 20 patients whose case histories were reviewed, follow-up information was incomplete or insufficient in nine. Eleven patients showed some degree of recovery. Seven of the 11 had a foot drop or required orthopedic appliances. Four were able to undertake limited activity; one was a soldier who returned to duty with 50% strength in the anterior tibial muscle; two were able to walk well, one with the aid of a tendon transplant.

Discussion

Certain important clinical features of ischemic necrosis involving the anterior tibial muscle have been discussed in the review of the literature. The patient reported in this article had a typical clinical course. There were some unanswered questions, however, in spite of an autopsy. The clinical impression of an ischemia following a bacteremia and embolus formation was not confirmed.

Because the patient had received reserpine, the role of this drug, if any, in the final illness must be considered.

Although reserpine is considered a tranquilizing agent, convulsions have been reported during its use. Barsa and Kline 12 observed that grand mal seizures, when present, occurred during the first six weeks of therapy. Seizures then ceased, although the drug was continued. This patient had received 0.25 mg. of the drug three times daily for seven months when his final illness was initiated with his first known grand mal seizure. An electro-encephalogram three days

after the seizure showed no pattern of diagnostic neurologic significance, and a search for toxic or circulatory factors was suggested. No additional electro-

encephalographic studies were done.

The pulmonary arteries at autopsy contained massive emboli. These could not be correlated with any other postmortem findings. That the necrosis of the anterior tibial muscle was initiated by an embolus or thrombus could not be ruled out. In the muscle fragment obtained at the time of exploration a minute artery with a recent thrombus was found. At the time of autopsy, examination was confined to the necrotic area.

Reserpine apparently does not affect the clotting of blood, either clinically or experimentally.¹⁸

SUMMARY

Acute ischemic necrosis of the anterior tibial muscle without prior, direct trauma is uncommon. In recent years 20 cases have been described following strenuous leg exercise, indirect injury, transfusions or in association with systemic illness.

The study of a 46 year old male with such a necrosis is reported here. The cause of his necrosis was in doubt, but the clinical course was typical of the cases already described.

The literature on the subject is reviewed briefly, with emphasis on the clinical aspects of etiology, differential diagnosis, pathogenesis and pathology, treatment and outcome.

The possible effects of reserpine on certain aspects of this patient's illness are mentioned.

The importance of early recognition and prompt treatment of this condition cannot be overemphasized.

ACKNOWLEDGMENT

The author is indebted to Dr. W. T. Liberson and Mr. Robert Smith for the photomicrograph, and to Mrs. Robert Garrow, librarian, for obtaining reference material. Dr. E. J. Manwell, Dr. D. R. Hayes and Dr. D. Jennison were the surgical consultants.

SUMMARIO IN INTERLINGUA

Es reportate le datos clinic e le constatationes necroptic in un caso typic de necrosis del musculo antero-tibial in un masculo psychotic de 46 annos de etate. Es presentate un revista del litteratura, con referentias special a certe aspectos clinic de 20 previemente reportate casos.

Acute necrosis ischemic del musculo antero-tibial pote occurrer in morbo systemic o post intense exercitios, insulto indirecte, o transfusion. Le declaration es acute, e le dolores que es sever, le tumescentia, e le erythema del gamba anterior es tosto sequite per extension del pede. Le apparentias suggere infection, sed le alteration pathologic es necrotic. Thrombosis o embolismo, spasmo arterial, alterationes chimic intra le musculo, augmento del tension in le compartimento antero-tibial, e alterationes in le arterias—omne istos ha essite considerate como factores in le production del syndrome.

Le tractamento es determinate per le stadio del morbo al tempore del diagnose. Mesuras preventive, incluse le appropriate conditionamento physic, es efficace. Reposo es indicate al tempore del declaration de dolor. Fasciotomia e chirurgia sympathic e vascular ha essite essayate. Mesuras chirurgic e orthopedic e mesuras de medicina physic es forsan necessari quando le musculo ha devenite firme e avascular.

Proque prompte diagnoses es rar, le majoritate del patientes se restabli con varie grados de defectuositate functional. Le patiente del presente reporto moriva. Esseva constatate al necropsia que ille habeva-a parte le necrosis ischemic antero-tibialmassive embolos pulmonar, congestion pulmonar, e pneumonia.

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CLINICALLY "INTERMEDIATE" THALASSEMIA DUE TO HYPERSPLENISM COMPLICATING THALASSEMIA MINOR: A CASE REPORT ILLUSTRATING RELIEF OF ANEMIA BY SPLENECTOMY *

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THALASSEMIA major and thalassemia minor are well recognized hematologic syndromes due to different degrees of an inherited defect in hemoglobin synthesis.

Thalassemia major is a severe childhood anemia (Cooley's anemia, Mediterranean anemia) with massive hepatosplenomegaly, jaundice from accelerated hemolysis of defective red cells, and bony changes secondary to an expanded,

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hyperplastic marrow. The red cells are hypochromic, microcytic and abnormally resistant to hypotonic saline. Target, oval and stippled red cells and normoblasts characterize the peripheral blood smear. The hemoglobin migrates closely with normal adult hemoglobin (hemoglobin A) on filter paper electrophoresis, but alkali denaturation reveals large amounts of slowly denaturing or "fetal" hemoglobin (hemoglobin F). 1

Thalassemia minor is usually an asymptomatic trait found in relatives of patients with the major form of the disease. Hypochromia, microcytosis and decreased osmotic fragility are also its hallmarks. Anemia is mild, and often a hypochromic polycythemia is discovered with red cell counts slightly higher and hemoglobin levels slightly lower than normal. The spleen tip may be palpable. Little or no increase in fetal hemoglobin is reported in the minor state.¹

The concept of thalassemia major as homozygous and thalassemia minor as heterozygous inheritance of a thalassemic gene was advanced by Caminopteros (quoted by Valentine and Neel ²) and strengthened by the latter's careful studies. However, the discovery of an occasional adult with thalassemia that seemed to fall between the major and minor pattern proved a drawback to its full acceptance. The earlier literature describing these intermediate syndromes has been summarized by March, Schlyen and Schwartz.³

A varying expressivity of the thalassemic gene could reconcile intermediate thalassemic syndromes with a heterozygous-homozygous mode of inheritance. Another possibility arose when the electrophoretically abnormal hemoglobins S, C, D and E were discovered, namely, that atypical thalassemia results from the interaction of one gene for an electrophoretically abnormal hemoglobin and one for thalassemia. Indeed, examples of hemoglobin S-thalassemia,^{4, 5, 6, 7} hemoglobin C-thalassemia ^{8, 9} and hemoglobin E-thalassemia ^{10, 11} were quickly found.

However, such double heterozygosity cannot account for all atypical thalassemia. Singer and his associates ⁸ have described two adults with "intermediate" thalassemia, George D. and his sister Daisy, who possess only hemoglobins A and F. Furthermore, the clinical findings in the double heterozygote states vary widely. Thus, hemoglobin S-thalassemia may present as a moderate hemolytic anemia resembling either sickle cell disease ^{4, 6} or thalassemia, ⁵ or, in contrast, as a mild disorder identified only by quantitative hemoglobin analysis. ⁷ Similarly, hemoglobin C-thalassemia has been discovered in a severely anemic child ⁹ and in two adults who exhibited only a microcytic erythrocytosis with slightly reduced hemoglobin levels. ⁸

The following patient is being reported to point out that hypersplenism complicating thalassemia minor may mimic "intermediate" thalassemia and should be considered in the evaluation of clinically atypical thalassemia.

CASE REPORT

The patient, a 34 year old man of Sicilian descent, had a normal, active childhood. At the age of 23 years, an enlarged spleen and a low hemoglobin level were discovered on a pre-induction examination. These findings did not prevent his induction into the Army, but soon resulted in a medical discharge.

He first entered this hospital in September, 1948, because of fractures sustained in a traffic accident. He had received five transfusions elsewhere for "shock and anemia" following the accident. He stated that he had been well except for brief spells of weakness and dizziness that had begun two years earlier.

TABLE 1
A Partial List of Joseph C's Blood Counts

Date	RBC m./mm. ⁸	Hgb. gm.%	Ht.	Retic. %RBC	MCV u ³	MCH γγ	MCHC %	WBC /mm.³	Platelets /mm.a
Sept. 1949	4.05	9.6	38		94	24	25	8,100	_
Nov. 1949	4.22	9.3	35	7.5	82	22	27	9,250	
Aug. 1950	3.52	8.4	33	10.7	94	25	25	8,900	150,000
June 1951	3.56	8.7	29	_	82	24	30	12,500	240,000
Jan. 1952	3.00	8.5	27	-	90	28	31	5,200	-
May 1952	3.52	8.9	31	6.3	88	25	29	6,400	
Apr. 1953	3.34	6.8	30		90	20	23	7,100	20,000
June 1953	3.16	7.9	28	7.0	89	25	28	6,600	90,000
July 1953*	3.79	9.2	36	-	92	24	26	8,000	36,000
				Splenecto	omy				
Oct. 1953	_	14.8	44		_		34	20,250	200,000
Aug. 1954	5.91	15.4	48	4.1	81	26	32	21,550	368,000
Feb. 1955	5.96	15.2	50		84	24	31	19,900	296,000
Sept. 1955	6.06	14.5	51	4.2	84	24	35	13,500	388,000

* The morning of operation and after seven weeks of cortisone.

Examination disclosed prominent cheek bones and a yellowish tint to his skin. His spleen extended about 4 cm. below the costal margin. His liver was not felt. There were fractures of his right clavicle and pelvis. A blood count revealed 4.1 million red cells; 9 gm. per 100 c.c. of hemoglobin; 8,450 white cells, with a normal

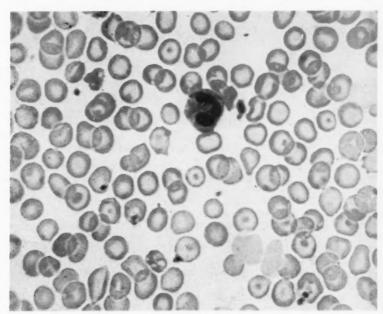


Fig. 1. Peripheral blood before splenectomy.

differential count; 140,000 platelets (direct Rees-Ecker method), and 6% reticulocytes. Roentgenograms of his skull, spine and pelvis did not show the bony changes of thalassemia. He received two transfusions and was discharged when his fractures permitted.

Between then and mid-1953 he was rehospitalized nine times because of complaints of fatigue, lassitude, weakness, dizziness and leg cramps. Repeated physical examinations disclosed a liver palpable 3 to 6 cm. below the costal margin, and a spleen that enlarged to reach the pelvic brim.

Some of his blood counts, selected to minimize the effect of transfusions, are listed in table 1. His red cells were very hypochromic, with many target cells and

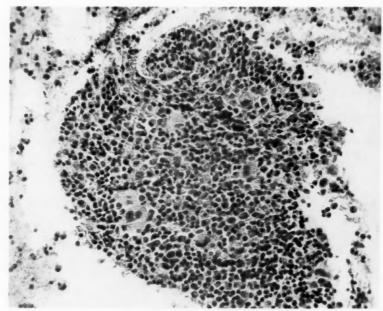


Fig. 2. Histological section of marrow particle before splenectomy showing marked hyperplasia with many megakaryocytes.

frequent oval and stippled cells (figure 1). Occasional normoblasts were seen on peripheral blood smears. Many hypochromic macrocytes were noted, and may have been the reason for a repeatedly normal mean corpuscular volume.

Saline fragility tests showed increased osmotic resistance, as on one occasion when hemolysis of the patient's cells began in 0.40% and was complete in 0.20% saline, with values of 0.44% to 0.30% for control cells. Two sickling tests were negative, as was a Coombs' test. Sternal marrow aspirations revealed hyperplasia of all marrow elements but particularly erythroid hyperplasia. Normoblasts were not found on a smear of a splenic aspirate. Liver function tests were negative several times except for a serum bilirubin level between 1 and 2 mg. %. A cholecystogram was normal.

The blood given after his accident introduced the patient to the idea of transfusions. From then on he sought transfusions for their "lift." Despite efforts to withhold blood, he received nine units between September, 1949, and May, 1952. In

January and again in May, 1952, chills and fever followed a transfusion. This led to the discovery of a high plasma titer of anti-c antibodies that persist in moderate titer to date.

He had bruised easily for years, but three platelet counts, the last in June, 1951, had been normal. In August, 1951, purpuric spots were discovered on his arms and his platelet count was found to be only 54,000 per cubic millimeter. Repeated platelet counts over the next two years were between 10,000 and 100,000 per cubic millimeter.

His condition deteriorated in the spring of 1953, with more severe purpura and a fall in his hemoglobin level to below 7 gm. per 100 c.c. A sternal marrow examina-

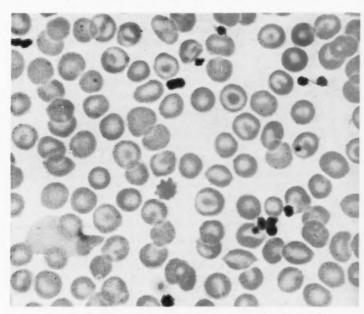


Fig. 3. Peripheral blood after splenectomy showing increased numbers of target cells and platelets.

tion revealed intense erythroid hyperplasia and abundant megakaryocytes (figure 2), but diminished platelet production. Seven weeks of 100 mg. of cortisone daily raised his hemoglobin level about 2 gm. per 100 c.c. but left his platelet count unaltered.

Splenectomy was performed on July 29, 1953. The spleen weighed 2,234 gm. and contained 7.6 gm. of iron. Microscopic examination showed hyperplastic follicles and prominent sinusoids with endothelial cell proliferation.

The patient withstood surgery well. His platelet count rose to 370,000 on the second, 500,000 on the third, and to almost 2,000,000 on the tenth postoperative day. By the twenty-seventh postoperative day it had fallen to 460,000 per cubic millimeter. Heparin was given while the platelet count was elevated.

Transfusions were unnecessary after splenectomy. His hemoglobin level gradually rose to reach 14 gm. per 100 c.c. within three months. His complaints vanished and, for the first time since we had known him, he felt well.

Two years have now elapsed since his splenectomy. His blood counts have continued to show a normal hemoglobin level, an elevated red cell count and a normal

platelet count (table 1). His red cells remain hypochromic, and target cells, prominent before splenectomy, now fill the smear (figure 3). An occasional normoblast can still be found in his peripheral blood, but these have not increased since splenectomy. A reticulocytosis of about 4% persists. A recent fragility study showed hemolysis beginning in 0.36% and still incomplete in 0.20% saline.

The patient's hemoglobin was studied electrophoretically after splenectomy, twice in this hospital and once by Dr. Phillip Sturgeon and Dr. William Bergren. Each time it migrated on filter paper as a single spot indistinguishable from hemoglobin A. Alkali denaturation disclosed a slightly elevated "fetal" hemoglobin concentration of 2.2%.

Family Studies: The patient's parents were both born in Palermo, Sicily. Neither knew of anemia or jaundice in any member of the family except the patient. They were examined in 1948 and 1949 and have since died of nonhematologic diseases.

Table 2
Summary of Studies on Joseph C's Family

Relation	Father		Mother	Sister L. S.	Brother C. C.	Brother Je. C.		Brother P. C.
Date	1948	1949	1948	1955	1955	1949	1955	1955
Hgb. (gm.%)	13.5	13.5	11.0	13.4	14.2	12.8	14.0	14.8
RCB (m./mm.3)	5.91	4.72	4.72	6.92	6.78	6.59	5.74	4.57
Ht. (%)	47	43	45	42	52	45	47	55
MCV (u³)	80	92	91	62	77	68	82	120
$MCH(\gamma\gamma)$	23	29	22	19	21	18	24	32
MCHC (%)	28	31	24	32	27	28	30	27
Retic. (%RBC)	0.2	1.2	0.1	3.6	10	2.0	3.8	
Saline frag.	decr.	norm.	_	decr.	decr.	decr.		norm.
Hgb. type by electro-								
phoresis	-	_	_	A	A	-	A	A
RBC morphology								
Hypochromia	?	+	+++	+++	+++	+++	++	
Target cells	+	-	+	++	+	+	_	
Oval cells	-		++	++	++	+	++	
Stippled cells		_	++	+	+	+	++	
Palp. spleen		+	not exam.	+	+	_		-

The patient is the youngest of seven children. One sister died in infancy, supposedly of pneumonia. One brother died at the age of 42 years of a bleeding peptic ulcer. Studies of the parents and other siblings are summarized in table 2.

The father's examination in 1948 disclosed a "hypochromic polycythemia," decreased red cell saline fragility, and occasional target cells. These findings, plus the splenomegaly discovered on reëxamination in 1949, strongly suggest thalassemia minor. His almost normal blood count in 1949 emphasizes for us how minor the abnormalities with the trait may sometimes be.

The mother's examination suggested that she also carried the thalassemic trait. Her red cells were markedly hypochromic. Her 1948 blood smear was recently reexamined, and many target, oval and coarsely stippled red cells were found. Unfortunately, her fragility study was inadequate.

Sister L. S., brother C. C. and brother Je. C. exhibit the "hypochromic polycythemia," decreased saline fragility and abnormal red cell morphology of typical thalassemia minor. Brother P. C. seems to be free of the thalassemic trait. Only hemoglobin A was found on filter paper electrophoresis of the siblings' hemoglobin.

DISCUSSION

Persistent hypochromia, target, oval and stippled red cells, and decreased red cell osmotic fragility in this patient of Sicilian descent made a diagnosis of some form of thalassemia almost certain. The discovery of typical thalassemia minor in his relatives confirmed it. The only finding unusual for thalassemia was his normal, rather than microcytic, mean corpuscular volume. Other instances of this are found in a report by Smith 12 and by Minnich and her co-workers. 13

The patient's presplenectomy findings, moderately severe anemia and splenomegaly in an adult, fitted neither thalassemia major nor thalassemia minor. They resembled Singer's definition of thalassemia intermedia. The suggestive evidence of the thalassemic trait in both parents made incomplete expressivity of a homozygous thalassemic gene a possible genetic explanation for this atypical clinical picture. An alternate explanation, the interaction of a thalassemic gene and a gene for an electrophoretically abnormal hemoglobin, was eliminated when his hemoglobin was found to migrate as a single spot indistinguishable from hemoglobin A.

The true explanation, hypersplenism, went unrecognized until he became thrombocytopenic, with a marrow full of megakaryocytes but inadequate in platelet production. Even then, splenic hyperfunction was not considered the main reason for his anemia. Its complete correction by splenectomy was a surprise.

Lichtman and his associates ¹⁴ called attention to extracorpuscular hemolytic mechanisms in thalassemia major. They reported shortened survival times of transfused normal red cells with lengthening following splenectomy. Smith and his co-workers ¹⁵ also found that splenectomy lengthened the survival time of normal red cells in thalassemia major and reduced transfusion requirements. Furthermore, these workers found a tendency for more severe extracorpuscular hemolysis in older patients. Minnich's group ¹³ described benefit in about one third of a splenectomized group of Thai patients with thalassemia major.

These studies replace the older view that splenectomy in thalassemia is valueless except for the mechanical relief it affords. Apparently, a patient with thalassemia major may develop enough splenic hyperfunction to warrant splenectomy. Of course, the improvement that follows will be limited, usually to the maintenance of a higher hemoglobin level, with fewer transfusions.

The complete relief of anemia that followed splenectomy in this patient makes us feel that his presplenectomy "intermediate" thalassemia was hypersplenism complicating thalassemia minor. His hemoglobin level could not have returned to normal if he were homozygous for the thalassemic gene. Normoblasts failed to increase in his peripheral blood, as they do after splenectomy in thalassemia major. Furthermore, his postsplenectomy "fetal" hemoglobin concentration was only 2.2%, as compared with the much higher values that persist after splenectomy in thalassemia major. ¹⁶

Therefore, this case report adds hypersplenism complicating thalassemia minor to the causes of clinically "intermediate" thalassemia. It points out again how the discovery of an intracorpuscular defect may draw attention away from an extracorpuscular reason for anemia. The increasing availability of simple methods for tagging red cells may simplify future evalution of such patients. Those with splenomegaly and shortened survival times of normal red cells may

benefit from splenectomy. The small group of adults with clinically "intermediate" thalassemia would seem in particular need of such studies.

Conclusions

A patient is described in whom clinically "intermediate" thalassemia was due to hypersplenism complicating thalassemia minor. This reason for atypical thalassemia warrants particular attention, for it is remediable. In this patient, splenectomy completely corrected a previously fixed anemia.

ACKNOWLEDGMENTS

We wish to thank Dr. Phillip Sturgeon and Dr. William Bergren for the hemoglobin analysis done in their laboratory. Mr. Herbert Carne did the analyses in this hospital. Mrs. Cyril Anderson did many of the blood counts.

SUMMARIO IN INTERLINGUA

Il existe un parve sed ben documentate gruppo de patientes con thalassemia de severitate intermediari inter thalassemia minor e thalassemia major. Tal casos es difficile a reconciliar con le hereditate heterozygotico-homozygotic de thalassemia. Alicunes ha essite explicate per le postulation de varie grados de expressivitate del gen de thalassemia. Altere casos es exemplos de heterozygoticitate duple, con un gen pro thalassemia e un altere pro un electrophoreticamente anormal hemoglobina, per exemplo S, C, o E. Le patiente describite in le presente reporto illustra como hypersplenismo como complication de thalassemia minor es ancora un altere mechanismo pro le production de thalassemia de severitate intermediari.

Le patiente esseva un homine de 34 annos de etate de ancestres sicilian. Su infantia esseva normal. Al etate de 23 annos, un splen de dimensiones allargate e basse nivellos de hemoglobina esseva discoperite. Examines effectuate inter 1948 e 1953 revelava un splen allargate usque al margine pelvic, un nivello de hemoglobina que variava inter 7 e 10 g, e frottis characterisate per hypochromia, anisocytosis, e cellulas a oculo de ave, oval, e granulate. Splenectomia esseva effectuate in 1953 a causa del disveloppamento de thrombocytopenia. Le splenectomia corrigeva non solmente le thrombocytopenia sed etiam le anemia. Durante le passate duo annos e medie, le nivello de hemoglobina del patiente ha remanite stabile inter 14 e 15 g.

Quando le patiente esseva restudiate recentemente, su aspecto clinic esseva illo de thalassemia minor. Typic formas de thalassemia minor esseva etiam discoperite in duo fratres e un soror del patiente. Electrophorese a papiro-filtro revelava solmente hemoglobina A in omne le quatro subjectos. Le concentration de hemoglobina fetal in le patiente esseva 2,2 pro cento.

Assi, hypersplenismo como complication de thalassemia minor pote producer un thalassemia clinicamente intermediari. Iste cause de thalassemia merita atypic attention special proque illo es remediabile.

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THROMBOTIC THROMBOCYTOPENIC PURPURA WITH EXTENSIVE HEMORRHAGIC GANGRENE OF THE SKIN AND SUBCUTANEOUS TISSUE: REPORT OF A CASE *

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No reports of this complication of thrombotic thrombocytopenic purpura were found in a review of the literature. Somewhat similar skin lesions were described, however, in two cases in which the patients eventually recovered. In the case reported by Jernigan and Farber 1 there were many features in common with the case herein reported. In the case they described, a 36 year old woman

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had recurrent malaise, chills, fever, thrombocytopenia, anemia, leukopenia, and hemorrhagic necrosis of the skin and subcutaneous tissue over a period of four years. There was good response to cortisone in a dosage up to 800 mg. daily. Skin biopsy demonstrated panniculitis, and no thrombi were seen. Typical lesions appeared at the site of procaine injection, and the possibility of a hypersensitive state was considered. In Dawson's 2 case of recurrent cutaneous and subcutaneous gangrene, the course was marked by fever and anemia, but there was no mention of thrombocytopenia, purpura or neurologic abnormalities. Thrombi were noted in microscopic examination of a section of the skin. The areas responded to local treatment, antibiotics, transfusions and skin grafting.

CASE REPORT

A 20 year old white married woman dependent was admitted to Madigan Army Hospital on October 24, 1953, because of profuse vaginal bleeding of one day's duration.

History of Present Illness: The last normal menstrual period had begun on September 11. There was excessive vaginal bleeding from September 25 until October 2, and again on October 23. Three days before admission small red spots appeared beneath the skin of the face, arms and legs. At that time there was also an episode of nosebleed and blood in the urine.

The patient had previously been well but had always had a tendency to bruise easily. She had had occasional nose bleeding with colds. There had been no recent exposure to drugs other than aspirin.

Family History: The mother of the patient had always bruised easily. A twin

sister and another sister were alive and well.

Past History: Three years before the patient had had a bout of urticaria for

which no cause was found. She had had a tonsillectomy at five years of age without excessive bleeding. She had been married for two and a half months.

Physical Examination: The patient was well developed and well nourished but pale and apprehensive. Blood pressure, 110/55 mm. of Hg; pulse, 100; temperature, 98.6° F. Innumerable petechiae were noted over the entire surface of the skin, as well as some areas of ecchymosis. Crusted blood was observed on the nasal septum, and there was bleeding from the gums. The lymph nodes were not enlarged. A soft basal systolic murmur was present. The liver and spleen were not palpable. On pelvic examination the only abnormality noted was blood in the vaginal vault.

Laboratory Data: The hematocrit was 19%. Leukocytes numbered 10,500 per cubic millimeter, with a normal differential. At the time of admission the urine was loaded with erythrocytes. A later specimen contained 1 plus protein, 3 to 5 leukocytes per high power field, and 3 to 5 granular casts per low power field. The specific gravity was 1.012. Platelets numbered 16,000 per cubic millimeter of blood. The result of a tourniquet test for increased capillary fragility was positive. Erythroid hyperplasia and slight myeloid immaturity were noted in material aspirated from the bone marrow. Megakaryocytes were present in possibly reduced numbers; their cytoplasm was finely granular, with the margins rounded off. The results of Coombs' test were repeatedly negative. No organisms grew on cultures of the blood. L.E. preparations on peripheral blood were negative. Cold agglutinins were present in a dilution of 1:128 on repeated occasions. Cryoglobulins were absent. The heterophil agglutination was negative. Protein content of the serum was 5.1 gm. per 100 c.c., with the albumin 2.4 gm. and the globulin 2.7 gm. The result of a cephalin flocculation test was negative, and the thymol turbidity was 0.7 unit. The icterus index was 3 units. No abnormality was observed in an x-ray film of the

chest. Low voltage QRS and T waves in Leads V5 and V6 were noted in an electrocardiogram late in the course of the illness.

Course in the Hospital: Transfusions of whole blood totaling 2,500 c.c. were given during the first week. Beginning October 28, cortisone was administered in daily doses of 300 mg., 200 mg. and 100 mg., which were then increased to 200 mg. daily, without appreciable effect on bleeding, platelet count or tourniquet test. Splenomegaly was first noted on October 29, with the edge felt just below the costal margin. On November 3 the spleen and three accessory spleens were removed. The pathologist reported myeloid metaplasia of the spleen, and on review of the tissue and sections of the bone marrow later in the illness, no evidence was found supporting the clinical diagnosis of thrombotic thrombocytopenic purpura. Cortisone was continued in daily doses of 100 mg, or more. Although the tourniquet test became negative, the platelet count did not exceed 26,000 per cubic millimeter. There



Fig. 1. Hemorrhagic gangrenous area of thigh with bullae formation.

White discoloration is from a lotion.

were continued vaginal bleeding and epistaxis in the immediate postoperative period, necessitating repeated blood transfusions. Although the platelet count subsequently fell and the tourniquet test again became positive, the bleeding tendency eventually lessened. Vaginal bleeding subsided in December. Despite the decreased bleeding, however, anemia persisted and blood transfusions averaging 1,000 c.c. a week were required to maintain the hematocrit generally at 30% or more. Moderate hypochromia, anisocytosis, poikilocytosis, polychromatophilia, nucleated erythrocytes, basophilic stippling and Howell-Jolly bodies were observed on examination of the blood.

At first the patient was afebrile. Although penicillin was given postoperatively, in November she began to have fever and tachycardia which persisted throughout the illness. The pulse rate ranged from 100 to 140. The temperature varied from 100° to 105° F.—generally from 101° to 104° F.—and it was not influenced by the antibiotics that were given, which included penicillin, chlortetracycline hydrochloride and oxytetracycline, or by the adrenal steroid therapy.

On November 27 severe visual impairment in the left eye developed, and retinal hemorrhages were evident. Cortisone therapy, which had been discontinued No-

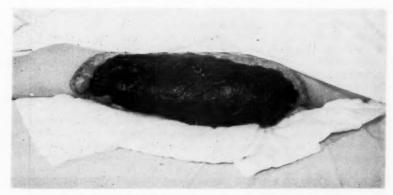


Fig. 2. Hard black eschar retracting and leaving a raw margin.

vember 17, was resumed and was followed by administration of corticotropin (ACTH) intramuscularly until December 30. The condition of the patient did not improve.

On December 2 an ecchymotic area appeared on the lateral aspect of the right thigh, followed by a similar lesion of the left. Initially ice packs were applied to one side. The areas rapidly increased in size. They had an elevated, indurated, reddish border about 1 cm. across. Material aspirated from the border was sterile on culture. The centers of the areas became dark purple to black. In dependent portions, bullae appeared and became confluent (figure 1). Meperidine was given



Fig. 3. Ulcerated area with hip joint capsule exposed after removal of eschar.

because of pain in the involved areas. Progression of the lesions had stopped by December 11. The areas were permitted to remain dry, and a thick, black eschar formed and then retracted, leaving a raw margin (figure 2). A similar, smaller lesion had also developed on one calf. On January 5 the eschars on the thighs were excised, leaving ulcerated areas extending to the deep fascia and exposing the capsule of the hip joint (figure 3). The areas were dressed frequently but never became suitable for skin grafting.

On December 21 the patient became unresponsive, and right hemiplegia and aphasia developed. She regained consciousness but never regained appreciable function, and from then on her condition progressively deteriorated. Ulceration

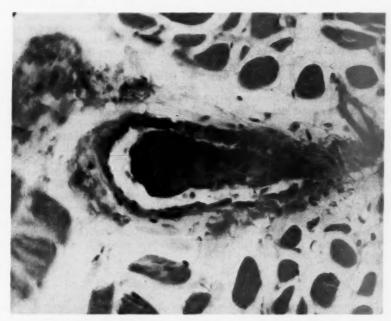


Fig. 4. Vascular lesion showing thrombus with overlying endothelium.

developed at sites of pressure, and the ulcers became confluent with the thigh lesions in some areas. On January 21 purpuric areas adjacent to urticarial wheals appeared on the thumb and on the chest. The latter disappeared, but the former ulcerated, possibly because of pressure.

For a period in January the hematocrit remained between 30 and 38% without any transfusions, and the tourniquet test became less positive. On January 11 platelets numbered 28,000, then increased to 48,000 by March 30. The change in number of platelets was not associated with any specific therapy. The hematocrit, maintained by transfusions except for the short period in January, generally varied from 30 to 40%.

In January a moderate systolic murmur, râles and hepatomegaly were noted. All became progressively more pronounced. In the latter part of March the patient began to have premature ventricular beats and bigeminy. She became more and more dyspneic and unresponsive, and died on April 4, 1954.

Postmortem Examination: Significant gross findings included two friable, redgray, mottled, verrucous lesions up to 1 cm. across, adherent to the closing margin of the anterior cusp of the mitral valve. The kidneys appeared congested. There was a large superficial area of softening in the brain involving half of the left temporal and parietal lobes. On section, a necrotic area occupied much of the left internal capsule and basal ganglia. The middle of three branches of the left middle cerebral artery was occluded by a gray mass; the third branch was partially obstructed but apparently recanalized. There was moderate enlargement of the mediastinal lymph nodes. The liver weighed 2,250 gm., and there was a uniform gray-red lobular mottling.

On microscopic section, the vegetations from the heart were observed to be composed of an eosinophilic, fibrillar and hyaline material having the appearance of a thrombus. Scattered throughout the myocardium were numerous small vessels, principally arterioles, filled with deeply eosinophilic masses in various stages of organization. Minimal changes were seen in the vessel wall, except for endothelial proliferation and occasionally a slight inflammatory reaction. There were numerous small infarcts in the myocardium, with both recent and old healed fibrous lesions. Similar lesions were seen in almost all tissues except the lungs. In a few instances eosinophilic masses only partially occluded the vessels, and appeared to be covered with endothelium and thus to be included within the intima (figure 4). The left cerebral artery was filled with thrombus and partially recanalized. In the kidneys many glomeruli appeared avascular, and whole glomeruli were replaced by connective tissue. A few glomerular capillaries contained thrombotic masses. An unusual feature was the presence of small, round, hyaline, basophilic bodies in glomerular capillaries of congested glomeruli. Elsewhere in the kidney there was moderate edema, with scattered foci of lymphocytes and small areas of fibrosis. The tubules presented changes including areas of atrophy, hyaline, red cell and pigmented casts, and areas of necrosis in the distal segments, with evidence of epithelial regeneration. Fatty metamorphosis was noted in the liver, and there was a scattering of myeloid cells suggesting extramedullary hematopoiesis. In bone marrow, hyperplasia of erythroid, megakaryocytic and myeloid elements was observed, and a few small arteries contained thrombi.

COMMENT

In a recent and exhaustive review Singer ⁸ discussed the many interesting and controversial aspects of thrombotic thrombocytopenic purpura, including its etiologic relationship to some hypersensitivity states such as the Shwartzman phenomenon, the relationship to the "collagen diseases," the question as to whether the pathologic lesion is a platelet thrombosis or primarily vascular in origin, and the mechanism of the thrombocytopenia and anemia.

An additional feature of this present case is the occurrence of a purpuric and ulcerating lesion adjoining an urticarial wheal. Despite the presence of cold agglutinins in high titer, the application of cold was not felt to be responsible for the gangrene, for in other areas the lesions had appeared spontaneously and progressed without the application of cold. Unfortunately, more thorough study of the anemia in the case here reported was not possible, but the persistence of anemia without significant bleeding and lack of response to transfusions suggested a hemolytic mechanism. In view of the satisfactory outcome in the somewhat similar case reported by Jernigan and Farber, one wonders what the response would have been to massive doses of adrenal steroids.

SUMMARY

Extensive gangrene of the skin and subcutaneous tissues developed in a 20 year old woman who had thrombocytopenic purpura, fever, anemia and hemiplegia. There was no significant response to splenectomy, transfusions, antibiotics or adrenal steroid therapy. Massive doses of cortisone were not employed, but are suggested should this complication be confronted again. At autopsy the pathologic features noted were those of the disorder described as thrombotic thrombocytopenic purpura.

SUMMARIO IN INTERLINGUA

Un femina blanc de 20 annos de etate moriva post un maladia de sex menses. Le declaration habeva essite marcate per sanguination vaginal e purpura, associate con thrombocytopenia. Therapia a cortisona esseva initiate, e le splen, que esseva levemente allargate, esseva excidite. Le condition del patiente non se meliorava. Post le operation, febre de 101 a 104 F se disveloppava e non subsideva con le administration de antibioticos, cortisona, e corticotropina. Anemia persistente, non attribuibile al sanguination, non respondeva a transfusiones. Tamen, il habeva un breve remission del thrombocytopenia. Le test de Coombs esseva uniformemente negative. Nulle cellulas lupo-erythematose esseva trovate a ulle tempore.

Sex septimanas post le declaration del morbo, progressive gangrena hemorrhagic del pelle e del tessutos subcutanee del femore superveniva. Cryo-agglutininas esseva presente sed nulle cryoglobulinas. Duo septimanas plus tarde, hemiplegia dextere e aphasia se manifestava. Le curso del morbo se deteriorava progressivemente.

Le necropsia revelava multiple thrombos de vasos minor in le majoritate del organos. Endocarditis nonbacterial thrombotic esseva notate. Le aspecto clinic e pathologic esseva un de purpura thrombocytopenic thrombotic, sed le complication de gangrena subcutanee ha non previemente essite describite.

Doses massive de cortisona es proponite si un simile problema es incontrate.

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EDITORIAL

POLIOMYELITIS IMMUNIZATION IN 1957

As THERE has been no dearth of editorial comment on the Salk antipoliomyelitis vaccine it might seem superfluous to add more, particularly as the most acute issues which arose in 1955 about this vaccine seem to have been more or less settled. The uproar which took place in the spring of 1955 has subsided and the experience of 1956 has satisfied most physicians in this country that the vaccine is safe and probably at least as effective as the Francis report originally demonstrated.¹ This report of the 1954 field trial indicated that what might still be called an "acute immunity" had been demonstrated, i. e. an immunity capable of reducing the incidence of paralytic poliomyelitis by from 60 to 80%, and one which has subsequently lasted at least two years. This is a great achievement. At that time (1954), many of the children were inadequately vaccinated according to the present day standards, so that with improvement of the Salk vaccine, and of the methods for its administration, 2 the future should give results as good if not better than those obtained three years ago. Furthermore, the safety problems seem to be well in hand. There have been no recorded post-vaccinal accidents of note since April 1955.

The story of the vaccine during 1955 and 1956, as reviewed week by week in the reports emanating from the Communicable Disease Center of the U. S. Public Health Service has furnished running commentaries on the effectiveness of the vaccine under different circumstances and the various types of reactions, allergic and otherwise which may follow its use. A critique has also come from the World Health Organization which includes some of the 1955 Canadian, European and South African experiences.³ In general this mass of data is nearly all favorable. It carries with it a strong degree of optimism which follows along with Salk's recent prediction, that indications "suggest that there need be little, if any, paralytic poliomyelitis in the United States in 1957 if all who are potentially susceptible are treated with vaccine that is now available." ²

As to the record, it would appear that as of January 1957, some 11,000,000 individuals in the United States had received one inoculation, 25,000,000 had received two, and 9,000,000 the required three inoculations to complete the full course. Of these 45,000,000 vaccinees, it has been estimated that 40,000,000 were under the age of 20, most of whom were under 10, and

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of school age. As poliomyelitis in the United States today is no longer regarded solely as a children's disease it has seemed wise to consider all individuals up to the age of 40, and in some states up to 45, as candidates for vaccination and this has posed a new program for most internists who have not previously been confronted with a task of this kind, so familiar to the pediatrician. Indeed this program which includes adult vaccination as an objective has now become something of a crusade with the National Foundation for Infantile Paralysis as its enthusiastic supporter. Health officers have joined in a nation-wide appeal to see that the program is adequately carried out, and the American Medical Association has given its endorsement. 4 So successful has this program been that it promptly

resulted in a temporary shortage of the vaccine.

In the face of this campaign which deserves support, one might say that this is no time for stock taking—that can come later. And yet this is the time to continue discussions which still concern some pediatricians, internists and microbiologists about the future effectiveness of this vaccine, particularly because the methods advocated today may not be the same as those to be followed tomorrow. These questions are: Will the coming year bear out the index of effectiveness in preventing paralytic poliomyelitis as being from 60 to 80%? Will this index be improved? What will be the ultimate duration of immunity against paralytic poliomyelitis which is conferred by the Salk vaccine, composed as it is of a killed, formalinized antigen? If immunity against paralytic poliomyelitis wears out, at what age will that occur? And how dangerous would this situation be in view of the fact that the older the age at which one acquires a poliomyelitis infection, the more severe is the infection apt to be? The large and increasing numbers of adult cases have been one of the recent disturbing features about poliomyelitis in the United States and Scandinavia. Such cases have been particularly common in young parents who, having reached this responsible age without having acquired natural immunity, run the extra risk of being infected by their children.

Time and careful observation will answer some of these questions. They are not sufficiently disturbing at the moment to warrant curtailment of the present vaccine program. Nevertheless, they should not be forgotten by physicians who are naturally aware of the unknowns in the situation. We come then to a consideration of the way in which the Salk vaccine is expected to work. On the surface one might be prompted to compare this vaccine (composed as it is of formalin inactivated polioviruses of the three antigenic types) with one of the other so-called killed vaccines whether they be composed of viruses or bacteria. Killed vaccines when injected into the body are expected to stimulate specific antibodies, and coincidently, immunity against the live agent to which the vaccinee may become naturally exposed.

It is recognized, of course, that such immunity is relative, and that it may

⁴ Poliomyelitis, J. A. M. A. 168: 653, 1957.

be inadequate when the vaccinee is exposed shortly thereafter to large doses of the specific infectious agent. Furthermore and in general, post-vaccinal immunity of this type eventually declines, leaving some vaccinees quite susceptible to infection following exposure to what may be small doses of the infectious agent. Thus the generalization has been made for years that most vaccines which involve the use of a killed antigen have to be given repeatedly, i.e. every few years, in order to keep the vaccinee's immunity in repair. Perhaps this will be the method eventually adopted for poliomyelitis.

However, the situation just described is not completely analogous to what happens with poliomyelitis immunization, for there are fundamental differences which should be emphasized here. Poliomyelitis is a disease in which the normal individual or child living in the United States usually sustains repeated subclinical or inapparent, though often widely spaced, infections during childhood, so-called alimentary infections. This may be due to one or more types of poliovirus, and, as a result of such repeated (homotypic or heterotypic) alimentary poliomyelitis infections, natural immunity in the normal child is usually acquired. It is common knowledge that only one out of a hundred or more cases of such subclinical or alimentary poliomyelitis infections may become severe enough to give rise to myelitis, which in turn is extensive enough to go on to produce paralysis. The primary aim then of the Salk vaccine against poliomyelitis is to bolster body defenses in an effort to reduce that fraction of 1:100 children who become paralyzed, almost as a complication of their alimentary infection, to 1:1000 or 1:10, 000. In other words its effect is to keep the vaccinee's immunity at a level so that when he becomes infected his "case" will be mild. Its effect is not that of preventing infection altogether. And this is fortunate for reasons to be mentioned presently.

Theoretically therefore, it might take a small amount of antigenic stimulus to protect the occasional child who in prevaccination days was due to become paralyzed, and this stimulus may be provided by a killed formalinized vaccine, given in one series of three doses, or conceivably in repeated series.

Consider, for instance, the background for immunization based on current views on the pathogenesis of paralytic poliomyelitis, 5, 6, 7, 8 which, although admittedly incomplete, can be described in terms of a hypothetical anatomical schema. For the virus to enter and penetrate into the body it must traverse various lines of defense. The first line of defense, let us say, is a barrier imposed by the intact mucous membranes of the mouth and/or the intestinal tract. The second line of defense is perhaps in the lymphoid

⁶ Sabin, A. B.: Pathogenesis of poliomyelitis. Reappraisal in the light of new data, Science 123: 1151, 1956.

⁷ Faber, H. K.: The evolution of poliomyelitic infection, Pediatrics 17: 278, 1956.
⁸ Horstmann, D. M.: Pathogenesis and immunity in poliomyelitis. The 1957 Gudakunst Lecture (unpublished).

⁵ Bodian, D.: Background for active immunization against poliomyelitis, Pediatrics 15: 107, 1953. See also: Mechanisms of infection with polioviruses, Ann. N. Y. Acad. Sc. (in press).

tissues which drain the throat and intestinal tract and which may localize the virus in submucous follicles or Peyer's patches, or in regional lymph nodes.9 There may also be other anatomical areas, as yet poorly visualized, where the virus may be multiplying in early stages of infection. From here, if the virus continues to multiply it may penetrate a third line of defense and enter the blood stream; there is still a fourth, the so-called blood-brain-barrier, and finally, conceivably a fifth, which represents these factors, poorly defined as they may be, which control the spread of virus within the central nervous system. Granted that some of these are theoretical considerations, and that it is possible for most of the middle lines of defense to be bypassed now and again by a mechanism which allows the virus to penetrate directly from a mucous surface into a neuron and subsequently along nervous channels directly into the central nervous system,7 still there is a good deal of information which indicates that viremia represents an important phase in the pathogenesis of paralytic poliomyelitis 10, 11, 12 and, if viremia can be blocked perhaps by antibody in the blood, the chances are greatly increased that the infection may remain localized in the alimentary tract or elsewhere within the forward lines of the body defenses.

According to this theory vaccine induced immunity in poliomyelitis, in which a killed vaccine is used, tends to be associated with the production of antibodies which may represent the strengthening of the third line of defense. To supplement the general defenses of the body are the repeated and naturally acquired post-vaccinal, alimentary infections against which Salk vaccine does not protect,13 and again one might say that this seems fortunate. For it is these repeated alimentary infections on which we may depend to keep our immunity against severe poliomyelitis infection in repair and which eventually might enhance the vaccinee's immunity so as to reduce the incidence of paralytic poliomyelitis not by 60 to 80% but by, let us say, 99%.

The discussion does not entirely end here because, if it turns out that natural infection is of great value in keeping the vaccinee's immunity in repair, should this matter of reinfection be left to pure chance or will the work on live attenuated virus vaccination enter the picture, as an adjunct or conceivably a substitute to the use of the killed vaccine? 14 This refers to the use of attenuated strains of polioviruses found or developed by Koprowski

⁹ Wenner, H. A., and Komitsuka, P.: On the presence of poliomyelitis virus in regional

lymph nodes, Pediatrics 16: 770, 1955.

¹⁰ Horstmann, D. M.: Poliomyelitis virus in blood of orally infected monkeys and chimpanzees, Proc. Soc. Exper. Biol. and Med. 79: 417, 1952.

11 Bodian, D.: A reconsideration of the pathogenesis of poliomyelitis, Am. J. Hygiene

^{55: 414, 1952.}

 ¹² Horstmann, D. M., McCollum, R. W., and Mascola, A. D.: Viremia in human poliomyelitis, J. Exper. Med. 99: 355, 1954.
 13 Lipson, M. J., Robbins, F. C., and Wood, W. A.: The influence of vaccination upon intestinal infection of family contacts of poliomyelitis patients, J. Clin. Investigation 35: 222. 1052.

¹⁴ Paul, J. R.: Properties of an "ideal" poliomyelitis vaccine, Bull. N. Y. Acad. Med. 32: 747, 1956. See also: Indications for vaccination against poliomyelitis, J. A. M. A. 162: 1585, 1956.

et al.15 and by Sabin 16 which are now being tested in children and adults by them, and by others in several study units. 17, 18 Such procedures, which may include the inoculation of killed vaccine followed some time later by the feeding of live attenuated virus, 14 are in an experimental stage and their practical use is for future consideration.

The final technic of immunization against poliomyelitis has probably not been evolved. In any event, however, in 1957 with the killed vaccine program well on its way in this country, not only is the prospect hopeful but there is every reason to believe that an invaluable start has been made in the elimination of the paralytic form of poliomyelitis infection. Internists as well as pediatricians have the chance to play an active rather than a passive role in this program.

JOHN R. PAUL, M.D.

15 Koprowski, H., Norton, T. W., Jervis, G. A., Nelson, T. L., Chadwick, D. L., Nelson, D. J., and Meyer, K. F.: Clinical investigations on attenuated strains of poliomyelitis virus, J. A. M. A. 150:954, 1956.

¹⁶ Sabin, A. B.: Present status of attenuated live virus poliomyelitis vaccine, J. A. M. A.
 162: 1589, 1956. See also Bull. N. Y. Acad. Med. 33: 17, 1957.
 ¹⁷ Dane, D. S., Dick, G. W. A., et al.: Vaccination against poliomyelitis with live virus vaccines. I. Trial of T. N. Type II vaccine, Brit. M. J. 1: 59, 1957.
 ¹⁸ Horstmann, D. M., Paul, J. R., Melnick, J. L., and Deutsch, J. V.: Infection induced

by oral administration of attenuated poliovirus to persons possessing homotypic antibodies, J. Exper. Med. (in press).

REVIEWS

Die Schutzimpfung gegen Poliomyelitis. A symposium of abstracts published by Behringwerk Mitteilungen. 291 pages; 16 × 24 cm. N. G. Elwert, Universitätsund Verlags-Buchhandlung, Marburg/Lahn. 1956. Price, DM 3.—.

This 290 page volume in German contains a series of abstracts of articles in which experts from various countries discuss developments of the polio vaccine in the United States and in their own countries. Laboratory data and immunological considerations with regard to gamma globulin, the Salk vaccine and the Sabin vaccine are discussed in detail. Descriptions of the field trials in the United States are given. Developments of interest in other countries are:

Germany: Germany has developed a vaccine (Behring Werk: Haas) on the same principle as the Salk vaccine. Aluminum hydroxide has been added and is said to increase antigenicity as well as to act as an additional safety factor. About 10,000 children were vaccinated in a field trial without any untoward effect. The antibody level obtained with the Behring vaccine is about the same as the antibody

level acquired by a natural infection.

Denmark: In view of very serious polio epidemics in recent years, Denmark proceeded early to produce a Salk-type vaccine. Variations from Salk's original procedure are described in detail. The vaccine was produced by the Serum Institute of the State. From April to June, 1955, 433,000 children, ages 7 to 10, were immunized. During the months April to September, 1955, there were only seven cases of poliomyelitis in Denmark. It was pointed out that this is not necessarily related to the effect of the vaccine as this was a year of extremely low prevalence following epidemic years. Up to date there was no case of poliomyelitis among the immunized children.

Union of South Africa: A formalized vaccine (Salk-type) has been prepared which appears to be safe and promises to be as effective as the Salk vaccine.

CANADA: Canada's experiences are described in detail.

England: Salk-type vaccines are being prepared by two commercial firms under the supervision of the Ministry of Health. Distribution will be limited to health departments. There will be no release of the vaccine for private practice. Plans call for voluntary immunization of 300,000 to 500,000 children, ages 1 to 9 before June, 1956. Any children who cannot be immunized during this period will be immunized in the fall. The producers of the vaccine deliver directly to all health departments in proportion to their needs. All cases of poliomyelitis must be reported to the Royal Statistical Department. The government pays for the vaccine.

Abstracts of a few of the papers by European authors and most of the articles

Abstracts of a few of the papers by European authors and most of the articles by American investigators listed in this volume may be found in abstract form in the "Periodical Annotated List" of "Poliomyelitis Current Literature" issued monthly

by the National Foundation for Infantile Paralysis.

A. T.-L.

The Biological Effects of Atomic Radiation (Summary Reports from a Study by the National Academy of Sciences). 108 pages; 28 × 21.5 cm. (paper-bound). National Academy of Sciences, National Research Council, Washington, D. C. 1956. Free distribution in any quantity.

The reports published herein represent the summation of the current findings of the committees which were established under the National Academy of Sciences to study the biological effects of atomic radiation in the fields of genetics, pathology, meteorology, oceanography and fisheries, agriculture and food supplies, as well as the problem of disposal and dispersal of radioactive wastes.

The aims, the essential facts, theories, arguments, and conclusions which can be drawn in the light of current knowledge are briefly but concisely reviewed and critically analyzed by each committee. The reader should appreciate that many of the tentative conclusions might be drastically modified when additional information based on progressive research and review becomes available. It should be realized that the present reports contain as much of the available and unrestricted information as could be compiled and summarized by the large assemblage of well known and respected scientific investigators.

The report of the Committee on Genetic Effects covers a wide and complicated field which to date has been filled to overflowing with unreasonable conjecture which has led to fear and frustration. This Committee very clearly presents the major concern with which it is faced: the complications, risks, and hardships which must be met in gaining useful knowledge and in reaching sensible decisions about future

policies.

The data concerned with the basic facts about genetics and genetic mutations caused by noxious stimuli (i.e., radiation) are presented in a manner that can be understood by readers of reasonable intelligence be they scientists or otherwise.

The other committees have compiled their findings in an equally interesting and

comprehensive presentation.

This is an excellent summation of the present knowledge of the biological effects of atomic radiation and should serve as a useful guide and basic information source for those especially interested in this subject. The publication is listed for free distribution.

ROBERT E. BAUER, M.D.

Diseases of the Nervous System. 5th Ed. By Sir Russell Brain, Bt., D.M. (Oxon.), F.R.C.P. (London). 996 pages; 22.5 × 14.5 cm. Oxford University Press, New York. 1956. Price, \$10.50.

Since 1933 this textbook has enjoyed popularity among medical students and general physicians, as well as neurologists. It is a well-rounded work, easy to read, with a succinct but complete description of the most important neurological entities. Its bibliography is not extensive but refers to basic publications.

In the new edition there has not been any marked change since there has been no very significant change in the field of neurology itself. The recognition and treatment of infectious diseases of the central nervous system and the chapters on inclusion body encephalitis, toxoplasmosis, and treatment of meningitis have been expanded and some new concepts in the etiology of some degenerative diseases are described.

Little attention has been given to some of the new diagnostic procedures that have proved very helpful in the recognition of neurological lesions in the last decade. Only a few lines are devoted to cerebral arteriography. However, a little more emphasis has been given to electroencephalography.

Basically this is a valuable neurological text for students and all physicians.

L. R. L.

Internal Secretions of the Pancreas. Ciba Foundation Colloquia on Endocrinology. Volume 9. Editors for the Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Cecilia M. O'Connor, B.Sc. 292 pages; 21 × 14 cm. Little, Brown and Company, Boston. 1956. Price, \$7.00.

Glucagon, alpha cells, insulin structure and action on tissues and cellular permeability, endocrine and hormonal interrelations are discussed in their physico-chemical and biological aspects by leading investigators in these fields from many countries,

Although a valuable summary of current ideas, the ultimate importance of the volume may have been well stated by Dr. F. G. Young, whose concluding remarks as chairman of the meeting were, "However gloomy the path may seem at times we may be sure that in meetings of this sort chinks of light will break through which will ultimately assist in the illumination of the whole interesting scene that lies before us."

Diseases of the Heart and Circulation. 2nd Ed. By Paul Wood, O.B.E., M.D. (Melbourne), F.R.C.P. (London); Director, Institute of Cardiology, London. 1005 pages; 25 × 16 cm. J. B. Lippincott Company, Philadelphia. 1956. Price, \$15.00.

The revised and enlarged American edition of Dr. Paul Wood's text on diseases of the heart and circulation is designed primarily for the postgraduate student of clinical cardiology. It will, however, also serve well as a reference book for anyone interested in disease which affects the cardiovascular system. A large part of the book is concerned with general abnormal physiology as relates to the recognition and diagnosis of heart disease. Special diagnostic procedures relative to the system involved are discussed as well as the more frequently and commonly used radiography and electrocardiography. The cardiopathies are grouped for discussion according to their various etiologies. Of particular note is the concern with incidence. Though the statistics are primarily those of England, the incidence in this country, as reported by our outstanding investigators, is given. Extensive references are given at the end of each section. A final, small section is given to psychosomatic cardiovascular disturbances.

The student of cardiology will find this an interesting and useful volume.

A. R.

The Treatment of Tuberculous Meningitis and Acute Pulmonary Tuberculosis. By Dr. Juan Torres Gost. 122 pages; 18 × 24.5 cm. Espasa Calpe, S. A., Madrid, Spain. 1955. Price, 90 pesetas.

The author has recorded his experience with the use of streptomycin and isoniazid in the treatment of 298 cases of tuberculous meningitis. Of these, 278 were cured and 20 died, for a mortality rate of 6.7%, a very commendable figure indeed.

The author's method of chemotherapy is quite different from that in general use in this country. He employs the principle of combined therapy, but not that of long term uninterrupted original treatment so popular here. He does not use streptomycin intrathecally, but he does employ intrathecal isoniazid almost universally.

His general plan of treatment of tuberculous meningitis in an adult would be as follows. Treatment is divided into three phases: the acute, the intermediate, and the complementary. The treatment of the acute phase lasts three months. Streptomycin 1 gm. per day is given for 45 intramuscular injections. Isoniazid is given by mouth in a dose of 400 to 600 mg. per day. Isoniazid is also given intrathecally, 30 mg. daily, for 35 to 45 days. The intrathecal dose may be increased to 50 mg. in severe cases, but this is seldom necessary. If at the beginning of the third month of treatment the patient has not become afebrile, 20 daily intravenous injections of 100 mg. of isoniazid are given or, in a very severe case, 250 mg. intravenously per day, reducing the oral dose of isoniazid accordingly. Only the exceptional case will require this variation in treatment.

Following three months of treatment with streptomycin and isoniazid the patient reaches the intermediate phase, which comprises two months of treatment with Conteben or Tibione 50 mg. twice daily, and PAS 12 gm. per day.

The complementary treatment then follows, immediately, consisting of 20 or 30 grams of streptomycin, 20 or 30 intravenous injections of isoniazid and 50 to 60 days of treatment with oral isoniazid. The patient then returns to work for six months, to return for a second course of complementary treatment followed by two more months of Conteben or Tibione plus PAS.

The author uses a similar therapeutic approach to the chemotherapy of acute pulmonary tuberculosis, without intrathecal isoniazid, of course, but emphasizing intravenous isoniazid. Again the combination of streptomycin and isoniazid in intensive doses, followed by Conteben and PAS, followed in turn by another course of streptomycin and isoniazid. Chemotherapy is then stopped for six months to be

resumed with another approximately two month course of streptomycin and isoniazid, followed by three more months of Conteben and PAS.

This is then prolonged combined chemotherapy for tuberculosis, using relatively high doses of streptomycin and isoniazid, and employing different drug regimens in succession, with eventual interruption and resumption of therapy rather than continuous prolonged original chemotherapy as we know it.

PATRICK B. STOREY

Koronarthrombose, Cor Pulmonale. Edited by Dr. Rudolf Thauer. 484 pages; 22.5 × 15.5 cm. (paper-bound). Verlag Dr. Dietrich Steinkopff, Darmstadt. 1955. Price, Brosch DM 56.-

As customary with the German Cardiological Society, specific topics are selected for discussion at the annual meetings. For the 1955 meeting, topics of coronary thrombosis and cor pulmonale had been selected. The initial paper on the pathology of coronary sclerosis, atheromatosis and thrombosis given by Mueller is distinguished in that there are only two non-German references (1936 and 1938), a remarkable piece of scientific myopia. Dr. D. E. Gregg presented a masterly discussion of "Some problems of the coronary circulation." The numerous factors influencing efficiency and quantity of coronary blood flow are clearly presented. A scholarly presentation of the clinical aspects by Schoen is followed by an interesting discussion of the significance of lipids and coagulation. Several interesting papers on blood protein formation, lipids and protein fractions, fibrinogen and fibrinolysis are supplemented by some with conventional discussions of statistical and therapeutic analysis.

The second part of the meeting was devoted to cor pulmonale and was opened by a superb discussion of the cardiac pathology by Kirsch. The dynamic problems of the complex entity "cor pulmonale" were most clearly and stimulatingly discussed by Kucher and Bolt. Denolin gave a masterly review of the clinical features and findings which in their printed form resemble more a monograph than a lecture. Indeed, it must have been one of the high points of the meeting. Some supplementary presentations on related topics rounded out the day. On the third day of the meeting miscellaneous papers were given. The most interesting among them was on cardiac efficiency under acute anoxic conditions. A new instrumental and conceptional approach is given. The abstracts of the German Cardiological Society indeed should prove a useful summary of the 1955 meeting. The book is well edited with numerous excellent reproductions and is to be recommended.

A. G

The Philosophy of Medicine. By William R. Laird, M.D. 64 pages; 14.5 × 22.5 cm. Education Foundation, Inc., Charleston, W. Va. 1956. Price, \$3.00.

This little book, which can be read in an hour or so of leisure time, and then referred to again, expresses the thoughts of a doctor on the attributes of the good doctor.

The section on the synthesis of individual experience related to the proper keeping of clinical records is an academic gem. Dr. Laird's discussion of esthetic values in medicine should be thoughtfully reconsidered by any doctor, but perhaps especially by him who is responsible in some measure for the education of physicians. The essence of the book, in this reviewer's opinion, is a discussion of the creation of more than a skilled super-technician in our modern doctor, of the development of a man wise in his own experience and study, of the true "guide, philosopher, and friend" to his patients.

Perhaps the comment is in order that the title is somewhat oversize for the size and contents of the book. It is certain that Dr. Laird did not intend to develop any truly philosophical treatise of the subject of medicine, and it is probable that the title will discourage many who would enjoy this book and profit from its perusal.

The book is recommended to all doctors, to doctors-to-be, and to all who are intimately concerned with doctors.

P. B. S.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

- Administration of Maternal and Child Health Services: Second Report of the Expert Committee on Maternal and Child Health. World Health Organization Technical Report Series No. 115. 28 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.
- The American Fluoridation Experiment. By F. B. Exner, M.D., and G. L. Waldbott, M.D.; edited by James Rorty. 277 pages; 21 × 14 cm. 1957. The Devin-Adair Company, New York. Price, \$3.75.
- The Care of the Expectant Mother. By Josephine Barnes, M.A., D.M. (Oxon.), M.R.C.P. (London), F.R.C.S. (England), F.R.C.O.G., Assistant Obstetrician and Gynaecologist, Charing Cross Hospital and Elizabeth Garrett Anderson Hospital, etc. 270 pages; 22.5 × 14 cm. 1956. Philosophical Library, New York. Price, \$7.50.
- Clinical Cardiopulmonary Physiology. Sponsored by The American College of Chest Physicians. Editorial Board: Burgess L. Gordon, M.D., Chairman, Philadelphia, Pennsylvania, Editor-in-Chief; Albert H. Andrews, Jr., M.D., Chicago, Illinois; Alvan L. Barach, M.D., New York, New York; John F. Briggs, M.D., St. Paul, Minnesota; Edwin R. Levine, M.D., Chicago, Illinois; George R. Meneely, M.D., Nashville, Tennessee; Hurley L. Motley, M.D., Los Angeles, California; Maurice S. Segal, M.D., Boston, Massachusetts; and Harold G. Trimble, M.D., Oakland, California. 759 pages; 26 × 18 cm. 1957. Grune & Stratton, New York. Price, \$15.75.
- Clinical Laboratory Methods, 5th Ed. By W. E. Bray, B.A., M.D., Consulting Laboratory Director, Martha Jefferson Hospital, Charlottesville, Virginia, etc. 731 pages; 20 × 12.5 cm. 1957. The C. V. Mosby Company, St. Louis. Price, \$9.75.
- Congenital Syphilis: A Follow-Up Study with Reference to Mental Abnormalities.

 Acta Psychiatrica et Neurologica Supplementum 93. By Bertil Hallgren and Einar Hollström; translated from the Swedish by Robert Hirschfeld, M.D.

- 81 pages; 24.5×16.5 cm. (paper-bound). 1954. Ejnar Munksgaard, Copenhagen. Price, Dan. Kr. 12.00.
- Current Therapy, 1957: Latest Approved Methods of Treatment for the Practicing Physician. Edited by Howard F. Conn, M.D.; Consulting Editors: George E. Burch, M. Edward Davis, Vincent J. Derbes, Garfield G. Duncan, Hugh J. Jewett, Perrin H. Long, Clarence S. Livingood, H. Houston Merritt, Walter L. Palmer, Hobart A. Reimann, Cyrus C. Sturgis and Robert H. Williams. 731 pages; 27.5 × 20 cm. 1957. W. B. Saunders Company, Philadelphia. Price, \$11.00.
- Death of a Man. By Lael Tucker Wertenbaker. 181 pages; 21×14 cm. 1957. Random House, New York. Price, \$3.50.
- The Doctor as a Witness. By John Evarts Tracy, Professor of Law (Emeritus), University of Michigan. 221 pages; 21 × 15 cm. 1957. W. B. Saunders Company, Philadelphia. Price, \$4.25.
- Dorland's Illustrated Medical Dictionary. 23rd Ed. Editorial Board: Leslie Brainerd Arey, Ph.D., Sc.D., LL.D., Robert Laughlin Rea Professor of Anatomy, Northwestern University; William Burrows, Ph.D., Professor of Microbiology, The University of Chicago; J. P. Greenhill, M.D., Professor of Gynecology, Cook County Graduate School of Medicine; and Richard M. Hewitt, A.M., M.D., Senior Consultant, Section of Publications, The Mayo Clinic. Philological Consultants: Paul J. Alexander, Ph.D., Associate Professor of History, Brandeis University; and Harry C. Messenger, M.D., formerly Instructor in Greek and Latin, Harvard University and Radcliffe College. Including Modern Drugs and Dosage, by Austin Smith, C.M., M.D., Editor, Journal of the American Medical Association; and Fundamentals of Medical Etymology, by Lloyd W. Daly, A.M., Ph.D., Associate Professor of Classical Studies, University of Pennsylvania. 1,598 pages; 26 × 17.5 cm. (leather-bound). 1957. W. B. Saunders Company, Philadelphia. Price, \$12.50.
- La Douleur et les Douleurs. Clinique des Maladies du Système Nerveux (Hôpital de la Salpêtrière). Publie sous la Direction du Pr. Th. Alajouanine, avec la collaboration de Mm. André-Thomas, J. Barbizet, G. Boudin, P. Castaigne, M. Critchley, R. Garcin, J. Gruner, J. Haguenau, R. Hazard, H. Hécaen, R. Houdart, J. Jacob, J. Lapresle, R. Leriche, Fr. Lhermitte, J. Lhermitte, L. Michaux, J. Morlaas, J. Nick, H. Piéron, J. Scherrer et R. Thurel. 345 pages; 25.5 × 17 cm. (paper-bound). 1957. Masson & Cie., Paris. Price, 2.400 fr.
- Expectant Motherhood. 3d Ed. By Nicholson J. Eastman, M.D., Professor of Obstetrics in Johns Hopkins University and Obstetrician-in-Chief to the Johns Hopkins Hospital. 198 pages; 19 × 12.5 cm. 1957. Little, Brown and Company, Boston. Price, \$1.75.
- Expert Committee on Addiction-Producing Drugs: Seventh Report. World Health Organization Technical Report Series No. 116. 15 pages; 24 × 16 cm. (paperbound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.
- From Witchcraft to World Health. By S. Leff, M.D., D.P.H., Barrister-at-Law; and Vera Leff. 236 pages; 22.5 × 14.5 cm. 1957. The Macmillan Company, New York. Price, \$4.50.

- Les Ictères par Rétention: Diagnostic Médico-Chirurgical. Par J. Caroli, avec la collaboration de A. Charbonnier, J. Étevé, A. Paraf et P. Ricordeau. 481 pages; 25 × 16.5 cm. 1956. Masson & Cie., Paris. Price, 6.700 fr.
- Liver, Biliary Tract and Pancreas. The Ciba Collection of Medical Illustrations. Part III of Volume 3: A Compilation of Paintings on the Normal and Pathologic Anatomy of the Digestive System. Prepared by Frank H. Netter, M.D.; edited by Ernst Oppenheimer, M.D. 165 pages; 31.5 × 24 cm. 1957. Commissioned and published by Ciba, Summit, New Jersey. Price, \$10.50.
- Meat Hygiene. World Health Organization Monograph Series No. 33. Contributors: V. E. Albertsen, R. Benoit, T. Blom, Phyllis G. Croft, C. E. Dolman, H. Drieux, R. I. Hood, M. J. J. Houthuis, A. Jepsen, H. H. Johansen, M. M. Kaplan, S. O. Koch, G. Scaccia Scarafoni, G. Schmid, F. Schönberg and H. Thornton. 527 pages; 24 × 16 cm. 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, \$10.00.
- Physiologic Principles of Surgery. Edited by Leo M. Zimmerman, M.D., Professor and Chairman of the Department of Surgery, Chicago Medical School, etc.; and Rachmiel Levine, M.D., Chairman, Department of Medicine, and Director, Department of Metabolic and Endocrine Research, Medical Research Institute, Michael Reese Hospital, etc. 988 pages; 25.5 × 16 cm. 1957. W. B. Saunders Company, Philadelphia. Price, \$15.00.
- The Problems of Vision in Flight at High Altitude. Agardograph 13. By Thomas C. D. Whiteside, Ph.D., M.B., Ch.B., Institute of Physiology, University of Glasgow, etc. 162 pages; 25.5 × 15.5 cm. 1957. Published for and on behalf of The Advisory Group for Aeronautical Research and Development, North Atlantic Treaty Organization by Butterworths Scientific Publications, London. Price, \$5.00.
- The Queen Charlotte's Text-Book of Obstetrics. 9th Ed. By the following obstetric surgeons to the hospital: G. F. GIBBERD, M.B., M.S., F.R.C.S., F.R.C.O.G., Obstetric Surgeon, Guy's Hospital; W. R. WINTERTON, M.B., F.R.C.S., F.R.C.O.G., Obstetric Surgeon, Middlesex Hospital; H. G. E. ARTHURE, M.D., F.R.C.S., F.R.C.O.G., Obstetric Physician, Charing Cross Hospital; BRIANT EVANS, M.B., B.Ch., F.R.C.S., F.R.C.O.G., Obstetric Surgeon, Westminster Hospital; KATHLEEN M. ROBINSON, M.D., F.R.C.S., F.R.C.O.G., Obstetric Surgeon, Royal Free Hospital; S. G. CLAYTON, M.D., M.S., F.R.C.S., F.R.C.O.G., Obstetric Surgeon, King's College Hospital; T. L. T. Lewis, M.B., B.Ch., F.R.C.S., M.R.C.O.G., Obstetric Surgeon, Guy's Hospital; J. S. Tomkinson, M.B., Ch.B., F.R.C.S., M.R.C.O.G., Obstetric Surgeon, Guy's Hospital; Charles D. READ, M.B., Ch.B., F.R.C.S., F.R.A.C.S., P.R.C.O.G., Director, Institute of Obstetrics and Gynaecology, University of London; Thomas Hunt, D.M., F.R.C.P., Physician, St. Mary's Hospital; A. White Franklin, M.B., B.Ch., F.R.C.P., Physician to the Children's Department, St. Bartholomew's Hospital; E. ROHAN WILLIAMS, M.D., F.R.C.P., F.F.R., D.M.R.E., Director, Radiological Department, St. Mary's Hospital; J. Murray, M.D., Director, Bernhard Baron Memorial Research Laboratories, Queen Charlotte's Hospital; G. W. B. JAMES, C.B.E., M.C., M.D., D.P.M., Honorary Consultant in Psychiatry, St. Mary's Hospital; and Geoffrey C. Steel, M.R.C.S., L.R.C.P., F.F.A.R.C.S., Consultant Anaesthetist, Royal Free Hospital. 547 pages; 24 × 15.5 cm. 1957. Distributed in the United States and possessions by Little, Brown and Company, Boston. Price, \$11.50.

- Radicular Syndromes, with Emphasis on Chest Pain Simulating Coronary Disease. By David Davis, B.S., M.D., Member, American Society for Clinical Investigation, etc. 266 pages; 20.5 × 14 cm. 1957. The Year Book Publishers, Inc., Chicago. Price, \$6.50.
- Rheumatic Diseases, Rheumatism and Arthritis. By Heinrich G. Brugsch, M.D., F.A.C.P., Assistant Professor of Medicine, School of Medicine, Tufts University, etc. 330 pages; 23.5 × 15.5 cm. 1957. J. B. Lippincott Company, Philadelphia. Price, \$10.00.
- Symposium on pH Measurement, Presented at the Fifty-ninth Annual Meeting, American Society for Testing Materials, Atlantic City, N. J., June 19, 1956. ASTM Special Technical Publication No. 190. 101 pages; 23 × 15 cm. (paper-bound). 1957. American Society for Testing Materials, Philadelphia. Price, \$2.50; to members, \$1.85.
- A Text-Book of Psychiatry for Students and Practitioners. 8th Ed. By Sir David Henderson, M.D. (Edin.), F.R.F.P.S. (Glas.), F.R.C.P. (Ed. and Lond.), Professor Emeritus of Psychiatry of Edinburgh University; and The Late R. D. Gillespie, with the assistance of Ivor R. C. Batchelor, M.B., F.R.C.P. (Ed.), D.P.M., Deputy Physician Superintendent, Royal Edinburgh Hospital for Nervous and Mental Disorders, etc. 746 pages; 22.5 × 14 cm. 1956. Oxford University Press, New York. Price, \$10.00.
- The Three Faces of Eve. By Corbett H. Thigpen and Hervey M. Cleckley. 308 pages; 21 × 14 cm. 1957. McGraw-Hill Book Company, Inc., New York. Price, \$4.50.
- Thyroid and Iodine Metabolism: Report of the Twentieth Ross Pediatric Research Conference. 77 pages; 23 × 15 cm. (paper-bound). 1957. Issued by Ross Laboratories, Columbus, Ohio. Available on request.
- Vitamin B₁₂ und Intrinsic Factor. Edited by Dr. H. C. Heinrich. 576 pages; 24.5 × 16 cm. 1957. Ferdinand Enke Verlag, Stuttgart. Price, Geheftet DM 75.; Ganzleinen DM 79.–
- Die Vitamine und ihre klinische Anwendung. By Dr. Med. W. Stepp, Dr. Med. J. Kühnau and Dr. Phil. Dr. Med. H. Schroeder. 975 pages; 24.5 × 16 cm. 1957. Ferdinand Enke Verlag, Stuttgart. Price, Geheftet DM 56.; Ganzleinen DM 59.40.
- Women Doctors of the World. By Esther Pohl Lovejoy, M.D., Ll.D., D.P.H. (Hon.), Chairman of the American Women's Hospitals Committee of the American Medical Women's Association, etc. 413 pages; 21.5 × 14 cm. 1957. The Macmillan Company, New York. Price, \$5.95.

ERRATUM

In the issue of January 1957, on page 170, line 24, the reference numbers "7, 15, 33" after the word "osteomyelitis" are incorrect and should be replaced by the single reference number "32,"

THE INDEX

TO THIS VOLUME HAS BEEN REMOVED FROM THIS POSITION AND PLACED AT THE BEGINNING OF THE FILM FOR THE CONVENIENCE OF READERS.

- Radicular Syndromes, with Emphasis on Chest Pain Simulating Coronary Disease. By David Davis, B.S., M.D., Member, American Society for Clinical Investigation, etc. 266 pages; 20.5 × 14 cm. 1957. The Year Book Publishers, Inc., Chicago. Price, \$6.50.
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COLLEGE NEWS NOTES

NEW ELECTIONS TO MEMBERSHIP IN THE AMERICAN COLLEGE OF PHYSICIANS

At the Thirty-Eighth Annual Session, held in Boston, Massachusetts, April 8–12, 1957, the following new members were elected. Those listed in FULL CAPITALS were elected to Fellowship; those in lower case were elected to Associateship.

HARRY NILS AKESSON Oakland, Calif. HENRY WILLARD ALLISON Akron, Ohio MARY D. AMES Harrisburg, Pa. GEORGE MABRY ANDERSON Lake Charles, La. Harvey Berle Ansell Portland, Maine Carl E. Arbesman Buffalo, N. Y. Frank Lynn Armstrong Mount Morris, N. Y. Norman James Ashenburg Rochester, N. Y. SAMUEL PHILLIPS ASPER, JR Baltimore, Md. ARNOLD RAYMOND AXELROD Detroit, Mich. Robert Glenn Axelrod Detroit, Mich.
Mortimer Eugene Bader New York, N. Y. Richard Arthur Bader New York, N. Y. Robert Liston Bailey, Jr. Richmond, Va. HENRY BAKER Boston, Mass.
Marvin Barnett
EDMUND GEORGE BEACHAM Baltimore, Md. Samuel Turkle Beall Vancouver, Wash. Earl Francis Beard Houston, Tex.
EVART MALCOLM BECK Indianapolis, Ind. Barkley Beidleman Pensacola, Fla. WILLIAM HARVEY BEINFIELD New York, N. Y.
JAMES CARROLL BELL Denver, Colo. Zachary Harold Benjamin Woodmere, L. I., N. Y. Robert Bernstein M. C., U. S. Army
WILBUR CARMEN BERRY M. C., U. S. Army JOHN GORDON BIELAWSKI Detroit, Mich. Oscar Bigman Detroit, Mich.
MAXWELL JACOB BINDERLos Angeles, Calif. (VA) WALTER PRESTON BITNERHarrisburg, Pa. LEWIS WILLIAM BLUEMLE, JRPhiladelphia, Pa.
Russell Sage Boles, Jr
JOHN GRIERSON BRAZER Omaha, Nebr. SIMONE BROCATO Columbus, Ga. Ralph Dexter Brown Everett, Wash.
BRADLEY CLAUDE BROWNSON San Mateo, Calif. Harry Herman Brunt, Jr Hammonton, N. J. Robert Legate Brutsche Springfield, Mo. (USPHS)

Louis Ray Cabiran	
Burton Marcus Cohen Elizabeth, N. J. MORRIS FRANK COLLEN San Francisco, Calif. JAMES ANTHONY COLLINS, JR Danville, Pa. ANDREW WILLIAM CONTRATTO Brookline, Mass. Herbert Kurtz Cooper, Jr Lancaster, Pa. Morton Charles Creditor Washington, D. C. Ernest Willoughby Creelman Bremerton, Wash. RICHARD IRVING CRONE M. C. U. S. Army Stanley Blandford Crosbie Grand Junction, Colo. (VA Charles Joseph Cross Columbus, Ohio Dan Crozier M. C., U. S. Army EDWARD ARMSTRONG CUSTER, SR Palo Alto, Calif.	A)
Michael Paul Dacquisto	

EUGENE JOSEPH ELLIS Los Angeles, Calif. Norman Ende Fresno, Calif. (VA) NELLES JOHN ENGLAND London, Ont., Can. WILLIAM WEBORG ENGSTROM Milwaukee, Wis. WILLIAM GEORGE ENSIGN Billings, Mont. Irwin Bernard Eskind Nashville, Tenn. EDWARD ROBERT EVANS Pasadena, Calif. Lloyd Roberts Evans Laramie, Wyo. Harold Eugene Everett Northampton, Pa.
MARSHALL JESSE FIESE Fresno, Calif. John Maurice Finlay Toronto, Ont., Can. Max Wolff Fischbach Philadelphia, Pa. Charles Irwin Fisher Chicago, Ill. HYMAN LOUIS FITTINGOFF Philadelphia, Pa. Francis Wilbur Fitzhugh, Jr. Atlanta, Ga. John Thomas Flynn New York, N. Y. Richard Bernard Foe Greeley, Colo. Donald Maxwell Fowell Stockton, Calif. Donald Thompson Foxworthy Hines, Ill. (VA) NATHAN FREDERICK FRADKIN Albany, N. Y. Herbert Frank South Bend, Ind. H. HAROLD FRIEDMAN Denver, Colo. Irving Abraham Friedman Oak Park, Ill. ALFRED MILLER FULTON, JR. Billings, Mont. JOHN KEITH FULTON Wichita, Kans. Edward Downing Futch, III Galveston, Tex.
Joseph Marion D. Gambescia

Charles Irving Hamilton, Jr	Concord, N. C. Brooklyn, N. Y. Atlanta, Ga. Auburn, Maine Houston, Tex. Lanton, Ohio Laston, Md. Lalem, Ore. Loncord, N. C. Littsburgh, Pa. Loose Jaw, Sask., Can. Licago, Ill. Loronto, Ont., Can. L. Louis, Mo. Lochester, Minn. Lonterey Park, Calif. Lorenton, N. J. L. C., U. S. Army Lenver, Colo. Latlanta, Ga. Lakeland, Fla. Laharlottesville, Va. Loodbridge, N. J. Littsburgh, Pa. Letroit, Mich. Littsburgh, Pa. Letveland, Ohio L. C., U. S. Army
Scott Russell Inkley	leveland, Ohio alveston, Tex. (USPHS)
CHARLES EUGENE JACKSON Charles Anthony Janda Robert Travis Jensen Mallace Norup Jensen Wallace Norup Jensen FRANK DONALD JOHNSON Fli Joseph Richard Johnson Ar Philip Carl Johnson, Jr. Robert Seedoff Johnson Sp JOSEPH EDWARD JOSEPHSON St. Benjamin Myer Kaplan William Karlinsky Harry Aaron Kashtan De HILLIARD JOEL KATZ Sa: Philip Gibbs Kaul Ka Richard Pierre Keating VIRGIL CRAIG KEELING Ro Maurice Leslie Kelley, Jr. Ro	ucson, Ariz. (VA) . C., U. S. Army tttsburgh, Pa. int, Mich. nn Arbor, Mich. (VA) klahoma City, Okla. (VA) bokane, Wash John's Newfoundland, Can. ines, Ill. (VA) finnipeg, Man., Can. etroit, Mich. nn Francisco, Calif. ansas City, Kans. dgewood, N. J. bokford, Ill.

William Francis T. Kellow	
Robert Chase Larimer Sioux City, Iowa Wilbur L. E. Larson Portland, Ore. Eunice Marie Lasché Tampa, Fla. Willoughby Lathem Pittsburgh, Pa. MORRIS LATTMAN New York, N. Y. (V. Samuel George Latty U. S. Air Force, M. CHARLES HARRIS LAWRENCE Chicago, Ill. Elbert Harold Laws Samuel Earnshaw LEARD Boston, Mass. HARRY CLAYTON LEAVITT Long Beach, Calif. (William Lessel Leet Providence, R. I. HAROLD JOHN LEHMUS Manchester, Conn. ALFRED ROBERT LENZNER Buffalo, N. Y. Louis Keiffer Levy Atlanta, Ga. Herbert Charles Lichtman Brooklyn, N. Y. LEONARD SANDFORD LINKNER Detroit, Mich. HARRY HOWARD LIPCON M. C., U. S. Navy MAURICE LEONARD LIPKIS Beverly Hills, Calif. Thomas Oliver Lohr Saginaw, Mich. Seattle, Wash. THOMAS JOSEPH LUELLEN Wichita, Kans. Emmett Stevenson Lupton Greensboro, N. C.	C.
James Robert Machan Fort William, Ont., C Esar Gordon Margolin Cincinnati, Ohio JEROME DAVID MARKHAM Richmond, Va. Leon Joseph Marks Boston, Mass. (VA) Richard Stanley Marton New York, N. Y. John Gregory Mayne Rochester, Minn. Robert Lowrey McClendon Louisville, Ky. *John Thomas McCoy Cedar Falls, Iowa KELLY TILSON McKEE Charleston, S. C. Charles Jeffrey McKitrick Columbus, Ohio JOSEPH HAMILTON McNINCH M. C., U. S. Army Robert Ligon McWhorter, Jr. Concord, N. C. * (M.C.) U.S.N.R.	an.

JOSEPH GOHEEN McWILLIAMSProvidence, R. I.
Gordon Campbell Meacham
Paul Albert Meredith
HAROLD MAURICE MESSENGERSan Diego, Calif.
Andrew Harry MeyerOakland, Calif.
Jean Claude D. MichelSeattle, Wash.
Alan Lawrence MichelsonLynn, Mass.
JAY WOLFE MILLERNew York, N. Y.
John Martin Miller Detroit, Mich.
M. Michael Bernard MillerNew York, N. Y.
Wade Norman Miller East Orange, N. J.
Richard Minton
DANA COVINGTON MITCHELL, JR Columbia, S. C.
BENJAMIN GERALD MORRISONNorthampton, Mass. (VA)
CHARLES SOL MORROW
Robert James Morton Seattle, Wash.
Howard Otis MottArlington, Va.
John Burroughs Moyer
John Henry Moyer, III
Edward William Mullin
Donal Patrick Murnaghan
Alex Thomas Murphey
FAY BALLENGER MURPHEY, JR Chattanooga, Tenn. Eldon Leonard C. Muttitt Regina, Sask., Can.
Eldon Leonard C. Muttitt
CHARLES FREDERICK NAEGELESan Jose, Calif.
Maurice Daniel Nast
Robert Phillip Natelson Sherman Oaks, Calif.
WILLIAM NEIL NEW
Robert Emmett O'Brien
JACQUES OLIVIER Sherbrooke, Que., Can.
David Terrell Overbey, Jr St. Petersburg, Fla. RICHARD RAPP OWENS
RICHARD RAPP OWENSMuncie, Ind.
John PageBrockville, Ont., Can.
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MARCEL PATTERSON
Camen Russell PaynterGreat Falls, Mont.
Carl Maxwell PearsonLos Angeles, Calif.
Edmund Daniel Pellegrino
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Anthony Joseph PesiriJamaica Estates, N. Y.
Brendan Pearse Phibbs
Roy Jacob PhilippBuffalo, N. Y. (VA)
Arthur Madison Phillips
Gabriel Pickar
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Ernest Richard Pitman
CHARLES EDWARD PORTERFairfield, Ala.
Robert Kennedy Portman
Robert Jay Priest Detroit, Mich.
EDWARD HUMPHREY REINHARDSt. Louis, Mo.
Arnold Seymour RelmanBoston, Mass.

Edmund Hare Reppert Hyman M. Robinson	.Brooklyn, N. Y.
Floyd Silas Beverly Rodman	
RIGBY CLYDE ROSKELLEY	Chi III
JOHN PUTNAM ROWELL	.Cnicago, III.
MANUEL J. ROWEN	St. Petersburg, Fla.
SAMUEL HAROLD RUBIN	A charge Dogle N. J.
Milton Emanuel Rubini	M. C. H. S. Army
Pasquale Arthur Ruggieri	Vineland N I
ALEXANDER RUSH	Dhiladalahia Pa
ALEXANDER ROSH	. I illiaucipilia, Ta.
Rolfe Wolff Salin	Ann Arbor Mich
WILLIAM DENNIS SCANLAN, JR	New York N. Y.
JEROME ARTHUR SCHACK	New York N Y
Harold Wilbur Schell, Jr	Norwich Conn.
TRUMAN GROSS SCHNABEL, JR	Philadelphia Pa.
CHARLES JOSEPH SCHREADER	Philadelphia, Pa.
Herbert Julian Schulman	Nashville, Tenn.
Arthur Schwartz	
Irving Leon Schwartz	
SOLOMON SCHWARTZ	
William Benjamin Schwartz	
MICHAEL SCIMECA	Brooklyn, N. Y.
John Pendleton Scully	Reading, Pa.
George Eliot Seiden	
Norman Keith Shachnow	New York, N. Y.
EDWARD SHAPIRO	Beverly Hills, Calif.
LORNE SHAPIRO	Montreal, Que., Can.
CHARLES SHEARD, JR	Stamford, Conn.
JOHN AUSTIN SHEEDY	M. C., U. S. Army
DANIEL JOSEPH SHEEHAN	M. C., U. S. Army
JACK ALLAN SHEINKOPF	Beverly Hills, Calif.
HYMAN ROCK SHEINTOCH	Brooklyn, N. Y.
EDWARD PAUL SHERIDAN	Denver, Colo.
JAMES BENJAMIN SHULER	M. C., U. S. Navy
Abraham Shulman	Montreal, Que., Can.
CHARLES ROSS SHUMAN	Philadelphia, Pa.
Robert George Siekert	
IRVIN S. SIGLIN	
Robert William Simpson	Seattle, Wash.
ALVIN SLIPYAN	Philadelphia, ra.
JACKSON ALGERNON SMITH	Omehe Nebr
Roy Cameron Smith	San Jose Calif
George Gottshall Snively	San Jose, Calif
Suzanne Agnew Snively	Sacramento, Calif
William Bray Spaulding	Toronto Ont Can
Fred Davis Spencer, Jr	Brownwood Tex
*GEORGE EDWARD SPENCER	Pittsburgh, Pa.
Norman Spitzer	Yonkers, N. Y.
Robert Ray Stahl	Cleveland, Ohio
John Frederick C. Stapleton	Holden, Mass.
* (MC) HCND	

^{* (}M.C.) U.S.N.R.

SAMUEL CHARLES STEIN HUGH STEPHENS Siegfried Stern Joseph Sternberg Alexander Raymond Stevens, Jr. Bertrand Lubell Stolzer Conrad Stritzler IRVING LEWIS STUTZ GEORGE COOKE SUTTON William Everett Swift WILLIAM PORTER SWISHER	. Palm Springs, Calif New Rochelle, N. Y Montreal, Que., Can Seattle, Wash Pittsburgh, Pa Jamaica, N. Y Pittsburgh, Pa Evanston, Ill New Haven, Conn.
HARRY TAUBE WILLIAM S. THAL Seymour Thickman ACORS WILLIAM THOMPSON JOHN JOSEPH THORPE JEROME NORMAN TOBER Eugene Jonas Towbin Beverly Todd Towery Charles John Tupper	. Toledo, Ohio . Sheridan, Wyo. . Falls Church, Va. . New York, N. Y. . Los Angeles, Calif. . Little Rock, Ark. (VA) . Louisville, Ky. . Ann Arbor, Mich.
Joseph Francis Uricchio	. Philadelphia, Pa.
Theodore Bertus Van Itallie	
Stanley Marvin Wald John Walter Walsh GEORGE FENTON WARNER HAROLD DRAPER WARREN Walter Wartonick ORLANDO HAROLD WARWICK Bascom Slemp Waugh RICHARD DENIS WEBER George Davis Webster, Jr. Richard Lawrence Wechsler WILLIAM H. WEHRMACHER WILLIAM WOLF WEISSBERG EDWARD JAMES WELCH Jay Justin Welch E(DWARD) BUIST WELLS Roe Edwin Wells, Jr. CHARLES ARTHUR WERNER BENJAMIN MORRILL WHEELER HAROLD NELSON WILLARD Samuel Clay Williams Walter Samuel Williams VICTOR WILLNER BENJAMIN NORMAN WILSON SIGMUND SAMUEL WINTON John Chase Wood James William Woolery Christian George Wornas Harold Alan Wurzel	Boston, Mass. (VA) San Francisco, Calif. Caribou, Maine Wilkes-Barre, Pa. (VA) Toronto, Ont., Can. Camden, N. J. Missoula, Mont. Philadelphia, Pa. Pittsburgh, Pa. Chicago, Ill. Elizabeth, N. J. Brookline, Mass. Canton, Ill. Erie, Pa. Boston, Mass. New York, N. Y. Edmonton, Alberta, Can. New York, N. Y. Winston-Salem, N. C. Fort Lauderdale, Fla. New York, N. Y. Tyler, Tex. Chicago, Ill. Philadelphia, Pa. Vancouver, Wash. Reading, Pa.

MORTON YOH	IALEM	 .New York, N. Y.
Daniel Eugene Y	ow	 . Concord, N. C.

Donald Charle	es Zavala .		El Centro, Calif.
Israel Zivin .			Chicago, Ill.
HERMAN B	ERNARD	ZURROW	New York, N. Y.

NEW LIFE MEMBERS

The following Fellows have become Life Members of the American College of Physicians:

- Dr. George A. Sherman, Lansing, Mich.
- Dr. Vincent Hernandez, Chevy Chase, Md.
- Dr. Joseph M. Hill, Dallas, Tex.
- Dr. George Johnson, Staten Island, N. Y.
- Dr. John A. Kinczel, Trenton, N. J.
- Dr. John H. Palmer, Montreal, P. Q.
- Dr. John M. Whitacre, Tacoma, Wash.
- Dr. Robert J. Williams, Warren, Ohio
- Dr. John L. Reynolds, Los Angeles, Calif.
- Dr. Myron August, Cleveland, Ohio
- Dr. Philip M. Gottlieb, Philadelphia, Pa.
- Dr. L. Minor Blackford, Atlanta, Ga.
- Dr. Herbert J. Schattenberg, San Antonio, Tex.
- Dr. Charles Silverberg, St. Louis, Mo.
- Dr. Sam A. Overstreet, Louisville, Ky.
- Dr. James Tesler, Brooklyn, N. Y.
- Dr. Louis R. Wasserman, New York, N. Y.
- Dr. Oliver C. Melson, Little Rock, Ark.

The listings are according to date of subscription.

Hawaiian members of the American College of Physicians, under the Governorship of Dr. Nils P. Larsen, conducted a regional meeting at Honolulu Wednesday, February 27, honoring particularly Dr. Edward Sayers of Auckland, New Zealand, President of the Royal Australasion College of Physicians. The meeting was held as a dinner meeting and had 20 of the local members in attendance. Following dinner there was a discussion and round table at which Dr. Sayers and the local members of the College considered various conditions in New Zealand and any variations in methods of therapy. Hypertension was one of the chief subjects of discussion.

Dr. Sayers stopped at Honolulu on his way to the United States to attend the Thirty-Eighth Annual Session of the College in Boston.

Dr. Ralph M. Truitt, (Associate), heretofore an Internist in the Turlock Medical Clinic, Turlock, California, has joined the staff of the Bangkok Sanitarium and Hospital in Bangkok, Thailand. He proposes to spend four and one-half years there.

The American Psychosomatic Society held its Annual Meeting at Atlantic City, May 4-5, 1957. Several Fellows of the American College of Physicians appeared on the Program of Panel Discussions.

Dr. Francis J. Braceland, F.A.C.P., Hartford, Connecticut, is currently President of the Association for Research in Nervous and Mental Disease, American Psychiatric Association, and (Chairman) of the National Health Forum.

Dr. Paul M. Seebohm, F.A.C.P., Iowa City, Iowa, addressed the Lancaster County Clinic Day at Lincoln, Nebraska, March 28, 1957, on "Chronic Lung Disease and Pulmonary Function Tests."

Dr. William B. Bean, F.A.C.P., Iowa City, has been elected a Vice President of the American Association for the Advancement of Science and Chairman of the section of Medical Sciences. Dr. Bean was a guest lecturer at Youngstown, Ohio, February 19, at the Heart Day Program, engaged in the clinics, made rounds, and gave a formal talk to the Youngstown Heart Association and Youngstown Academy of Medicine on "Chest Pain." On March 30, Dr. Bean addressed the California Academy of Medicine on "The Medical Career—Why We Study Medicine and Why We Specialize," at San Francisco, Calif. On April 1, he addressed the Palo Alto Medical Center on "Useful Lessons from Rare Diseases."

Dr. Maurice S. Segal, F.A.C.P., Clinical Professor of Medicine, Tufts University School of Medicine, and Director of the Department of Inhalation Therapy and Lung Station (Tufts) of the Boston City Hospital, delivered a series of lectures between January 28 and February 2, 1957, at various Los Angeles institutions, including the Children's Hospital of East Bay (Oakland), Oakland Medical Society, Highland Hospital (Oakland), and Los Angeles County Medical Association. On March 13, he addressed the Woman's Medical College of Philadelphia in connection with a Symposium on clinical pulmonary physiology.

Colonel James H. Forsee, (MC), U.S.A., F.A.C.P., is the new Deputy Commander and Chief of Professional Services of the Walter Reed Army Hospital.

Captain Lester J. Pope, (MC), U.S.N., F.A.C.P., Head, Medicine and Surgery Branch, Professional Division, Bureau of Medicine and Surgery, recently participated in the symposia on military medicine at San Antonio and Houston, Texas.

Dr. Lewis Cohen, (Associate), Detroit, Michigan, presented a paper entitled "Electrovasography in the Study of Peripheral Vascular Dynamics," at the National Biophysics Conference in Columbus, Ohio, on March 5, 1957.

Dr. Hans Popper, F.A.C.P., has been appointed Director of the Department of Pathology at The Mount Sinai Hospital, New York, and Professor of Pathology, College of Physicians and Surgeons, Columbia University. Dr. Popper was for many years director of the Department of Pathology, Cook County Hospital; scientific director of the Hektoen Institute for Medical Research; and Professor of Pathology, Northwestern University Medical School, all in Chicago. Dr. Popper has succeeded Dr. Paul Klemperer.

Dr. J. H. Peters, F.A.C.P., left the Veterans Administration on May 15, 1957, to accept a position as Assistant Medical Director for Research of the American Heart

Association. Dr. Peters was formerly at the Veterans Administration Hospital in Atlanta. His new address will be 44 East 23rd Street, New York City.

Dr. H. Harold Gelfand, (Associate), New York City, addressed the Allergy Staff of the Bellevue Medical Center on March 1, 1957, his subject being "The Botany of Hay Fever."

Dr. Mayer A. Green, F.A.C.P., Pittsburgh, Pa., participated in the graduate instructional course in allergy of the American College of Allergists at Chicago, Illinois, March 17-19, 1957. His presentation was on "Drug Allergy—Excluding the Respiractory Tract." Dr. Green was elected to the Board of Regents of the American College of Allergists recently for a term of three years.

Dr. Dana W. Atchley, F.A.C.P., New York City, delivered the annual Phi Lambda Kappa Lecture of the New York University College of Medicine on April 30, the title of his lecture being, "Science in Medical Education." Dr. Atchley is professor of clinical medicine at the College of Physicians and Surgeons, Columbia University.

Dr. W. A. Sodeman, F.A.C.P., Professor and Chairman of the Department of Medicine, University of Missouri Medical Center, was Moderator of a panel discussion on the program of a series of postgraduate medical education sessions held in the auditorium of the University of Missouri Medical Center, February 28, 1957. The program as a whole was devoted to a symposium on diabetes mellitus, using as the subject, "Some Present-Day Concepts in the Pathogenesis and Management of Diabetes Mellitus."

Dr. Roscoe L. Pullen, F.A.C.P., Dean and Professor of Medicine, University of Missouri School of Medicine, Columbia, Mo., entertained during March a Planning Sub-Committee from the University of Puerto Rico School of Medicine, among whom were Dr. Rurico S. Diaz-Rivera, F.A.C.P., Professor and Head of the Department of Medicine and Dr. Enrique Koppisch, F.A.C.P., Professor and Head of the Department of Pathology.

Dr. A. Carlton Ernstene, F.A.C.P., Cleveland, Ohio, addressed a luncheon meeting of the Wisconsin Society of Internal Medicine at Milwaukee, May 9, his subject being "Differential Diagnosis of Pain of Coronary Heart Disease."

The Wisconsin Society of Internal Medicine is rapidly expanding its program into relevant studies affecting the fees and services of internists in that state. Questionnaires have been distributed among the internists of Wisconsin, in an effort to determine the usual time involved for a single office visit, the charge for a single office visit, and the time involved for a complete diagnostic examination. This Society is responsible for the statement, "The practice of Internal Medicine consists of supplying the patient with the benefits of superior skills in the fields of diagnosis and medical therapeutics. The public is slowly coming to realize the value of the thoroughness of this type of medical care. The patient is less aware of the time involved and the training necessary to supply this service. Appropriate remuneration is often colored by the existing practice of the small charges for the usual 'office visit' which is merely a brief examination and treatment of a presenting complaint, or the more insidious acceptance of the office visit as a 'loss leader' in favor of the more remunerative surgery a large practice will yield."

RESIDENCIES IN PHYSICAL MEDICINE AND REHABILITATION

Approved residencies in physical medicine and rehabilitation are available at New York University-Bellevue Medical Center, beginning July 1, 1957. American graduates with approved internships are eligible for OVR Fellowship, starting at \$3,400.00 per year with added dependency allotment. Applications should be made to Joseph G. Benton, M.D., Institute of Physical Medicine and Rehabilitation, 400 East 34th Street, New York 16, N. Y.

The University of Texas Postgraduate School of Medicine and the Texas Diabetes Association presented a lecture course on Diabetes Mellitus at San Antonio, Texas, on March 22 to April 5, 1957. Of the eighteen members of the faculty, nine were Fellows and three were Associates of the American College of Physicians.

The Eighteenth Annual Meeting of the Society for Investigative Dermatology will be held at the Belmont Plaza Hotel in New York City, June 1 to 2, 1957.

ONE MILLION DOLLARS IN 1956 FOR AID TO EDUCATION AND RESEARCH

Grants made by Charles Pfizer & Co., Inc., and the Pfizer Foundation to educational and medical institutions for individual financial aid, fellowships and support of scientific research in 1956 totalled approximately \$1,000,000. Of this amount, students, resident physicians and pharmacy interns received \$330,000 through their individual institutions for aid in the completion of their education. Medical schools, veterinary colleges, pharmacy colleges and hospitals throughout the country benefited under the program.

The sum of \$359,000 was granted to universities, hospitals, and agricultural experiment stations, both here and abroad, for advanced studies in medical, chemical, and agricultural technology.

The following members of the College participated in the 1957 Industrial Health Conference at St. Louis, Mo., April 20–26, 1957; Paul Gross, M.D., F.A.C.P., Pittsburgh, Pa.; Paul E. Foldes, M.D., (Associate). Cincinnati, Ohio; Howard Rusk, M.D., F.A.C.P., New York City; Daniel Riordan, M.D., (Associate), Hamburg, N. Y.; R. Enmet Kelly, M.D., F.A.C.P., St. Louis, Mo.; Lemuel McGee, M.D., F.A.C.P., Wilmington, Del.; Daniel H. Goldstein, M.D., (Associate), New York City; O. A. Sander, M.D., F.A.C.P., Milwaukee, Wis.; and William B. Thompson, M.D., (Associate), Oklahoma City, Okla.

Dr. Louis L. Perkel, F.A.C.P., Dr. Harry J. Perlberg, F.A.C.P., and Dr. Thomas J. White, F.A.C.P., all of Jersey City, were recently appointed Professors of Gastroenterology, Radiology, and Medicine, respectively, at Seton Hall College of Medicine, Jersey City, New Jersey. Each will continue as a director of his respective department at the Jersey City Medical Center.

Dr. Wesley Spink, F.A.C.P., Professor of Medicine at the University of Minnesota and College Governor for the State of Minnesota, was the honored guest at the Dallas Southern Clinical Society meeting in March, 1957. He was sponsored by Dr. Martin S. Buehler, F.A.C.P., who is the incoming President of the Texas Geriatrics Society and who resides in Dallas, Texas.

"Therapy in Internal Medicine" was the title of a medical symposium sponsored by the Department of Internal Medicine of Iowa Methodist Hospital and held at Des Moines, Iowa, May 11. The Roster of speakers included Dr. J. Earle Estes, F.A.C.P., Rochester, Minn.; Dr. Paul M. Seebohm, F.A.C.P., Iowa City, Iowa; Dr. Wesley W. Spink, F.A.C.P., Minneapolis, Minn.; and Dr. Samuel G. Taylor, F.A.C.P., Chicago, Ill.

Rear Admiral Bartholomew W. Hogan, F.A.C.P., Surgeon General of the Navy, participated in the Fifth Annual Conference on Atomic Energy in Industry, March 14–15, 1957, at Philadelphia. Admiral Hogan was Chairman of the Round Table Session on Health and Safety Problems.

Dr. Allan M. Goldman, F.A.C.P., New Orleans, La., has been promoted from Instructor to Clinical Assistant Professor of Medicine at Tulane University of Louisiana School of Medicine. He has also been promoted to Senior in Medicine at Touro Infirmary.

Dr. Sidney Friedlaender, F.A.C.P., Detroit, Mich., was one of the invited participants in the panel discussions on "Present Concept of Therapy in Allergy with Cortisone and Allied Drugs" and "Drug Sensitivities," sponsored by the Honolulu County Medical Society at Honolulu, Hawaii, February 15, 1957.

The Third Annual Forum of the Woman's Medical College of Pennsylvania, Philadelphia, was held March 13, 1957. Those participating in the Symposium of Clinical Pulmonary Physiology included Dr. George R. Meneely, F.A.C.P., Nashville, Tenn.; Dr. R. Drew Miller, (Associate), Rochester, Minn.; Dr. Maurice S. Segal, F.A.C.P., Boston, Mass.; Dr. John B. Youmans, F.A.C.P., Nashville, Tenn.; Dr. Stewart Wolf, F.A.C.P., Oklahoma City, Okla., and Dr. Arthur M. Master, F.A.C.P., New York City. "Health in the Headlines" contributors included: Dr. John B. Youmans, "World Nutrition Problems"; Dr. H. J. Tumen, Philadelphia, Pa., "Emotions and the Gastrointestinal Tract"; Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa., "One May Live Happily with Heart Disease"; Dr. Stewart Wolf, "The Relation of Life Stress to Cardiovascular Symptoms of Disease."

AUDITOR'S REPORT, YEAR ENDING DECEMBER 31, 1956

To the Board of Regents American College of Physicians, Inc. 4200 Pine St. Philadelphia 4, Pa.

Mr. E. R. Loveland, Executive Secretary

Dear Sir:

I have examined the accounts of the

AMERICAN COLLEGE OF PHYSICIANS, INC.

for the year ending December 31, 1956, and the accompanying statements, including the Balance Sheet at December 31, 1956, the analyses of the General Fund and Endowment Fund and the Statement of Income Account for the calendar year 1956 are in accordance with the Books of Account, and in my opinion present fairly the financial position at December 31, 1956 and the results of operations for the calendar year 1956, in conformity with generally accepted accounting principles applies on a basis consistent with that of preceding years, and subject to the following comments:

Cash: The Cash was properly accounted for, was confirmed by direct correspondence with the following depositories, and the Petty Cash verified:

Girard Trust Corn Exchange Bank, Philadelphia Provident Trust Co., Philadelphia Royal Bank of Canada, Montreal Petty Cash	29,542.82 4,740.56
	\$64,903.68

Accounts Receivable: The Accounts Receivable were examined and found to be less than one year old and appear to be collectible. The detailed accounts receivable were in agreement with the control account. No requests for confirmation of the accounts were mailed.

Investments: The securities were accounted for by direct correspondence and the income for the period under review was verified. The investment transactions are recorded properly in the general books of account and in the Investment Ledger, which is in agreement with the investment accounts of the General Ledger.

General: The changes in the amount of the Endowment Fund and the General Fund during the year 1956 are as follows:

	Balance Jan. 1, 1956	Dec. 31, 1956	Increase
Endowment Fund	10,000.00	\$ 490,810.37 10,000.00 20,100.00	\$26,152.50
General Fund Restricted Funds Willard O. Thompson Fund Residency Revolving Loan Fund	. 793,372.80 1,810.67 10,341.58	801,497.18 2,136.92 10,466.58 40,000.00	8,124.38 326.25 125.00 20,000.00
	\$1,320,282.92	\$1,375,011.05	\$54,728.13

The Executive Secretary has analyzed the income of the Annals of Internal Medicine according to Volume, so that the income and expenses are stated according to the year of publication, with the exception of Volumes of prior years, which are closed out and not carried in an inventory account, with the sales properly credited to the General Fund according to the date of sale.

General Comments: The prepaid insurance at December 31, 1956, was not set up as a deferred expense; the other deferred and accrued items were verified; the charges to the Furniture and Equipment Accounts represent proper additions to the account, and the allowances for depreciation appear to be adequate. A depreciation reserve account has been set up for the Headquarters Building in accordance with the action of the Board of Regents at the meeting of December 12, 1937, which provided that depreciation on the building should be taken into account at the rate of \$1,000.00 per year and increased in 1949 to \$2,000.00. A depreciation reserve account has been set up for 404–12 S. 42nd Street at the rate of \$500.00 per year. The footings and extensions of the inventory were verified.

All ascertainable liabilities have been included in the Balance Sheet.

All recorded receipts from dues, initiation fees, exhibits, advertising, sales of publications, etc., were properly deposited in banks and all disbursements, as indicated on the vouchers, cancelled checks and bank statements were properly recorded in the books of account.

Respectfully submitted,

(Signed) DAVID ROBIN, Auditor

Balance Sheet, December 31, 1956 General Fund

1. 46,	No. 6		COLLEGE	NEWS	NOTES			CIXXXV	/11
476 47	23,	554.12 1,325.41 257.39		25,705.97	15,819.44	\$196,349.27 801,497.18 \$997,846.45		\$490,810.37 3,043.70 10,000.00 20,100.00	\$534.420.65
Liabilities	Accounts Fayable Deferred Income: Advance Subscriptions, Annals of Internal Medical Cine, Volumes 46 to 52 1957 Exhibits, paid in advance	Restricted Finds: Income on James D. Bruce Fund Investments Income on A. Blaine Brower Fund Investments Income on Willard O. Thompson Traveling Scholarship Fund	Elizabeth Archbold Bowes Travening Scholarships ships Mead Johnson Postgraduate Scholarships 10,500,00 Portrait-Photo Fund Salvabana Regional Mecting 70,83 Mid-West Regional Mecting 142,22	Southeastern Kegional Meeting 145,507 1956-57 Reserve Fellowship Fund 13.358.34 Residency Revolving Loan Fund 24,300.00 Less Advances on above 24,300.00	National Institute of Health Grant \$43,100,00 Less Expenses 27,280.56 Study of Hospital Standards in Medicine Ap- Sacionication	Funds	Endowment Fund Liabilities Current:	Endowment Fund, Principal \$490,810,37 Accrued Income, Due to General Fund 3,043.70 James D. Bruce Fund 10,000,00 A. Blaine Brower Fund 20,100,00	Willard O. Thompson Traveling Scholarsing Fund
GENERA	\$ 60,652.96 21,533.14 425.00 1.379.50	3,043.70 2,544.94 784,729.84 555.00 \$874,864.08	8,864.10	84,882.32	16,091.23	13,144.72	Endowm	\$ 4,250,72 \$27,126,23 3,043.70	\$534,420.65
Assets	Current: Cash in Banks and on Hand \$60,652.96 Accounts Receivable \$21,533.14 American Air Lines Pledons and Frames 1,379.50		Deferred: Expenses, 38th Annual Session \$ 8,569.69 Advertising, Volume 46	Fixed: College Headquarters: Real Estate Less Demeciation 28,000,00	Furniture and Equipment \$ 29,087.21 Less Depreciation 12,995.98 404-12 S. 42nd Street:	Keal Estate Less Depreciation 1,000,00	Current:	Cash Investments at Book Value Acrued Income on Investments	

Summary of Operations for the Calendar Year 1956

Income:		
Annual Dues Initiation Fees Subscriptions, Annals of Internal Medicine Advertising, Annals of Internal Medicine Income from Investments, General Fund (including Accrued) Income from Investments, Endowment Fund (including Accrued) Dividend on Perpetual Insurance Deposit Income on Sale of Annals Volume Files Postgraduate Courses (Balance) Profit on Sale or Maturity of Securities, General Fund Profit on Equipment Traded in Interest on Time Deposits Rent, 404-12 S. 42nd Street	18,425.00 168,817.15 117,802.05 38,029.78 23,097.31 60.00 265.57 4,805.34 10,495.85 25.00 292.50	
Thirty-seventh Annual Session:		
Exhibits 37,412.31 Guest Fees 5,277.50	42,689.81	
Collection and Exchange Keys, Pledges and Frames	222.23 184.88	\$518,138.07
Expenses:		
Salaries Communications Office Supplies and Stationery Printing Maintenance Traveling Expenses Editorial Assistance Cumulative Index Miscellaneous College Headquarters, Maintenance, Taxes, Insurance, etc. Depreciation on College Headquarters Building Depreciation on 404–12 S. 42nd Street Associated Hospital Service Regional Meetings Depreciation on Furniture and Equipment John Phillips Memorial Award Investment Counsel Service and Security Custodian's Fee Employees' Pension Fund Advertising Discounts Loss on Sale or Maturity of Securities, General Fund Joint Commission on Accreditation of Hospitals Academic Regalia Interlingua Translations 1955 Directory 1956 Supplement Loss on Sale of Equipment Traded in Thirty-seventh Annual Session—Special Expenses: Committee on Panel Discussions \$ 217.60 Committee on Publicity 1,400.00 Committee on Ladies' Entertainment 305.97 Convocation 1,981.18	\$106,999.73 18,960.73 4,366.49 155,967.54 415.24 42,454.59 1,650.00 6,058,99 7,075.18 10,284.47 2,000.00 500.00 307.47 5,228.46 3,195.08 250.00 14,397.50 2,733.87 540.94 4,328.34 116.73 100.00	
1956 Convocation Gown Rental 501.50		

Income, Brought Forward			\$518,138.07
Expenses, Brought Forward		\$399,724.44	
37th Annual Session, Special Expenses, Brought Forward Registration Rent Clinic Expenses Projection Service College Booth Expenses Public Address System Clinical-Pathological Conferences Reception and Dinner for New Members 1956 Banquet Concert Program Scientific Exhibits Speakers Assembly Room Televised Clinics	1,017.44 5,909.69 125.00 475.30 167.06 246.00 100.00 1,604.38 465.74 881.25 2,525.78	\$ 22,292.47	
404-12 South 42nd Street: Maintenance Heat, Light, Gas and Water Taxes Insurance Miscellaneous Total Expenses	19.64 515.10 176.72 2.25		
Net Income for 1956 Credited to General Fund			\$ 93,896.16

(The Auditor did not include in this statement the operations for the Study of Hospital Standards in Medicine—the appropriation of \$37,000.00; the Grant from National Institutes of Health of \$43,100.00; or the expenditures of \$27,280.56.)

INVESTMENTS

BONDS

At December 31, 1956

	At December 31, 1930	Fun	nds
Par Value	Bonds	Endowment	General
\$15,000	Allied Chemical & Dye Corp., Deb. 31/2's, 1978	\$ 14.850.00	
10,000	Allied Chemical & Dye Corp., Deb. 3½'s, 1978	,,	\$ 9,962.50
13,000	Aluminum Co. of Canada, 37%'s, 1970		13,276.25
12,000	American Gas & Electric Co., Deb. 33/8's, 1977	12,270.00	
13,000	American Tel. & Tel., 37/8's Deb., 1990		12,902.50
12,000	American Tel. & Tel., 37/8's Deb., 1990	11,910.00	,
9,000	American Tobacco Co., 3's, 1969		
14,000	American Tobacco Co., 3¼'s, 1977	14,087.50	
10,000	Arkansas Power & Light Co., 1st, 3½'s, 1982		10,367.00
15,000	Baltimore & Ohio Equip. Trusts, 31/8's, 1962		14,999.85
9,000	Carolina Clinchfield & Ohio Rwy. Co., 1st Mort. 4's, "A", 1965	9,465.70	- 19
10,000	Chesapeake & Ohio Rwy, Equip, Trust Certs., 27/8's,	1,10216	
	1965		9,854.18
12,500	Columbus Gas System, Deb. 33%'s, "C", 1977		12,500.00
2,500	Columbus Gas System, Deb. 33%'s, "C", 1977	2,500.00	
10,000	Connecting Rwy. Co., 1st, 31/8's, "A", 1976	9,600.00	
10,000	Connecting Rwy. Co., 1st, 31/8's, "A", 1976	,	8,925.00
6,000	Consolidated Edison Co. of New York, 3's, 1981	5,970.00	-1, -0100
	Forwarded	\$ 90,068.44	\$ 92,787.28

INVESTMENTS—Continued

Bonds

		Fur	ids
Par Value	Bonds	Endowment	General
	Brought Forward	\$ 90.068.44	\$ 92,787.28
25,000	Consolidated Edison Co. of New York, 41/4's, 1986	*	25,218.75
25,000	General Electric, 3½'s, 1976		24,937.50
25,000	General Motors Acceptance Corp., Deb. 37/8's, 1961.	25.593.75	24,231.30
10,000	General Motors Corp., Deb. 3¼'s, 25 yr., 1979	10.162.50	
20,000	Hydro Electric Power Commission of Ontario, Can.,		
20,000	3½'s, 1979	20,675.00	
15,000	New York Central Railroad Second Equip. Trust	20,075.00	
15,000	Certe 336's 1965		14,794.13
5,000	Certs., 3%'s, 1965 Oregon-Washington RR & Nav. Co., Ref. 3's, "A",		14,7 24.10
5,000		5,300.00	
4,000	Oregon-Washington RR & Nav. Co., Ref. 3's, "A",	3,300.00	
4,000	1960		4.240.00
20,000	1960 Pennsylvania RR Equip. Trust Cert., 2½'s, 1961		19,700.00
15,000	Pittsburgh & Lake Erie RR, Equip. Trust Certs.,	•	19,700.00
15,000	3's, 1964		14,723.04
25,000	Public Service Electric & Gas. 4%'s, 1986		25,314.25
10,000	Reading Co., Equip. Trust Certs., "U", 3½'s, 1963		9,999.90
3,700	Scott Paper Co., Deb. 3's, 1971		3,700.00
10,000	Seaboard Airline Equip. Trusts, 2%'s, "L", 1966		9.746.80
10,000	Service Pipeline Co., Deb. 3.20's, 1982	10,025.00	9,740.60
15,000	St. Louis, San Francisco RR Co., Equip. Trusts,	10,025.00	
15,000	27%'s, 1962		14025 52
10,000	Texas & New Orleans RR Co., 1st & Ref., 31/4's,		14,935.53
10,000	"B". 1970	10,458.60	
12,000	II S Trensum Ponds 21/2 "C" March 1 1057	10,456.00	12,000.00
10,000	U. S. Treasury Donds, 272 8, G, March 1, 1957	10,000.00	12,000.00
16,000	U. S. Treasury Donds, 272 8, G, March 1, 1957	16,000.00	
7,000	II S Treasury Donds, 272 S, G, July 1, 1957	7,000.00	
10,000	II S. Treasury Donds, 2728, G., February, 1938	10,000.00	
6,000	U. S. Treasury Bonds, 272 s, G, March 1, 1959	6.000.00	
5,000	U. S. Treasury Bonds, 272 S, G, July 1, 1959	0,000.00	5,000.00
2,500	U. S. Treasury Bonds, 272 s, G., July 1, 1937	2,500.00	5,000.00
2,500	U. S. Treasury Bonds, 272 S, G, March 1, 1900	2,500.00	
2,500	U. S. Treasury Bonds, 272 S, G, January 1, 1901	2,500.00	
14,000	U. S. Treasury Bonds, 272 S, G, January 1, 1902	14,000.00	
20,000	U. S. Treasury Donds, Series K, September 1, 1950	14,000.00	20,000,00
12,500	"B", 1970 U. S. Treasury Bonds, 2½'s, "G", March 1, 1957 U. S. Treasury Bonds, 2½'s, "G", March 1, 1957 U. S. Treasury Bonds, 2½'s, "G", July 1, 1957 U. S. Treasury Bonds, 2½'s, "G", February, 1958 U. S. Treasury Bonds, 2½'s, "G", February, 1959 U. S. Treasury Bonds, 2½'s, "G", July 1, 1959 U. S. Treasury Bonds, 2½'s, "G", July 1, 1959 U. S. Treasury Bonds, 2½'s, "G", March 1, 1960 U. S. Treasury Bonds, 2½'s, "G", January 1, 1961 U. S. Treasury Bonds, 2½'s, "G", January 1, 1961 U. S. Treasury Bonds, Series "K", September 1, 1956 U. S. Treasury Bonds, Series "K", December 1, 1966 U. S. Treasury Bonds, Series "K", Junuary 1, 1967 U. S. Treasury Bonds, Series "K", Junuary 1, 1967 U. S. Treasury Bonds, Series "K", Junuary 1, 1967 U. S. Treasury Bonds, Series "K", Junuary 1, 1967 U. S. Treasury Bonds, Series "K", June 1, 1967 U. S. Treasury Bonds, Series "K", June 1, 1967 U. S. Treasury Bonds, Series "K", June 1, 1967 U. S. Treasury Bonds, Series "K", June 1, 1967	12 500 00	20,000.00
10,000	U. S. Treasury Donds, Series K., January 1, 1907	12,500.00	10,000,00
9.000	West Pour Floatric Co. D.F. Coll Tr. 21/2- 1074	0 541 27	10,000.00
2,500	West Penn Electric Co., D.F., Coll. Tr., 3½'s, 1974 U. S. Treasury Bonds, 2½'s, "G", June 1, 1962		
2,500	U. S. Treasury Donds, 272 S, G, June 1, 1902	2,500.00	
	Total Bonds	\$267 324 66	\$307,097.18
	Total Dollas	φωυ/,324.00	φυυν,υνν.18

INVESTMENTS

STOCKS

At	December	21	1956

	At December 31, 1956	F	,
		Fu	nds
Shares	Stocks	Endowment	General
328	American Gas & Electric Corp., Common	\$ 4,035.03	
525	American Gas & Electric Co., Common		\$ 6,403.0
100	American Smelting & Refining Co., 7% Pfd	18,867.80	, ,
33	American Telephone & Telegraph		
110	American Telephone & Telegraph		19,437.5
300	Armstrong Cork Company		8,868.9
800	Atchison, Topeka & Santa Fe RR	9,770.74	
40	Atchison, Topeka & Santa Fe RR		2,442.6
519	Atlantic City Electric Company, Common		6,488.6
174	Atlantic City Electric Company, Common	1,655.75	
100	Bethelehem Steel, 7% Pfd	16,825.75	
260	Campbell Soup Co., Common	10,330.06	
15	Campbell Soup Co., Common		595.9
150	Chase Manhattan Bank of New York, Common		5,725.0
142	Chase Manhattan Bank of New York, Common	5,039.67	
210	Commonwealth Edison Corp., Common	5,596.38	
210	Commonwealth Edison Corp., Common Consolidated Edison Co. of New York		7,593.2
300	Consolidated Edison Co. of New York		9,979.8
100	Consumers Power Co., 4½'s, Cum. Pfd		11,287.5
150	Continental Insurance Co. of New York, Common	0.000.00	3,445.0
100	Continental Insurance Co. of New York, Common	2,375.09	44 40 40
306	Dow Chemical Co.		16,684.0
200	E. I. du Pont de Nemours, Common	(10101	8,714.8.
268 -	Fidelity-Phoenix Fire Insurance Co., Common	6,124.94	10 122 5
287	First Pennsylvania Banking & Trust Co	2 170 27	10,132.50
77	First Pennsylvania Banking & Trust Co	3,170.27	2 = 7 = 7
300	General Electric Co., Common	2 700 00	3,571.78
300	General Electric Co., Common	3,780.96	2 504 5
300	General Motors Co., Common	2 272 72	3,594.5
180	General Motors Co., Common	2,272.73	7 920 20
200 268	B. F. Goodrich Tire Co., Common		7,830.39 8,632.27
300	Gulf Oil Corp., Common		
346		10,369.89	19,890.20
50	Insurance Company of North America, Common	8,169.00	
200	International Harvester Co., 7% Pfd	0,109.00	6.605.79
250	International Paper Co., Common		9,313.12
50	Kaiser Aluminum & Chemical Co., 4.75 Cum. Pfd	2,638.56	2,010.11
350	Kaiser Aluminum & Chemical Co., 4.75 Cum. Pfd	2,000.00	18,434.23
200	Kennecott Copper Corp., Common		10.918.2
100	Mead Corp., 4¼'s, Cum. Pfd.		9.308.25
100	Mead Corp., 4¼'s, Cum. Pfd.	9,796.05	2,000.20
425	Middle South Utilities, Inc.	8.209.41	
375	Middle South Utilities, Common	0,202.11	8,192.33
312	Monsanto Chemical Co.		8,556.66
156	Monsanto Chemical Co.	5,056.95	0,000.00
208	National City Bank of New York	7,989.85	
193	National City Bank of New York	1,0000	8.844.29
400	New York State Electric & Gas Co.		9,816.02
50	Niagara Mohawk Power Corp., 3.90% Pfd		5,067.50
			-,
	Forwarded	\$147,921.12	\$256,374.52

INVESTMENTS-Continued

STOCKS

	SIUCKS		I	Funds
Shares	Stocks		Endowmen	t General
	Brought Forward .		\$147,921.13	\$256,374.52
200	Mellon National Bank & Trust Co		4-11,	17,075.00
200	Niagara Mohawk Power Corp., Comm	on		4,969,92
400	Niagara Mohawk Power Corp., Comm	on	9.944.61	
100	Niagara Mohawk Power Corp., 3.60%	Pfd		
300	Ohio Edison Co., Common		20,200.00	13,010.25
200	Owens-Illinois Glass Co., Common			9,845.45
100	Owens-Illinois Glass Co., Common		5,364.40	
400	Pacific Gas & Electric Co., 6% Pfd		0,001.10	13,557.14
130	Pacific Gas & Electric Co., 6% Pfd		4.907.09	
200	Panhandle Eastern Pipe Line Co., 4%	Cum. Pfd	20,271.43	
210	Pennsylvania Power & Light Co., Com	mon	8,512.85	
340	Pennsylvania Power & Light Co., Com	mon	0,010100	11,456,43
200	J. C. Penney Co., Common			17,143.94
136	Philadelphia Electric Co., Common			4,046.50
320	Philadelphia Electric Co., 1.00 Div. Pre	f. Common	7.791.13	
400	Phillips Petroleum Corp., Common	ar common rrrr		5,286.27
210	Pittsburgh Plate Glass Co., Common .			10,805.93
300	Scott Paper Co., Common			10,547.48
200	Sherwin-Williams Co., Common			19,829.78
200	Southern California Edison Co., 4.23%	Cum. Pfd		5,180.62
300	Southern California Edison Co., Commo	on no		15,308.43
1200	Standard Oil Co. of New Jersey, Comn	10n		10.964.16
100	Tennessee Gas Transmission Co., 4.60%		10.924.64	
200	Tennessee Gas Transmission Co., 4.60%		10,000	19,680.70
800	Texas Company, Common		12,382.11	27,000110
200	Tide Water Asso. Oil, 1.20 Cum. Pfd.		,000	5,558.15
300	Trans-American Corp			12,858.75
225	Union Carbide & Carbon Co		6,146.98	12,000110
75	Union Carbide & Carbon Co		.,	3,019.88
290	U. S. Fidelity & Guaranty Co			11,113.36
100	U. S. Fidelity & Guaranty Co U. S. Steel Corp., 7% Cum. Pfd		15,450.20	,
	Total Stocks		\$259,801.57	\$477,632.66
Total In	vestments:			
	Endowment Fund	General Fund		Total
	ls\$267,324.66 ks\$259,801.57	\$307,097.18 477,632.66	\$	574,421.84 737,434.23

\$527,126.23

\$784,729.84

\$1,311,856.07

OBITUARIES

RECENT DEATHS OF A.C.P. MEMBERS

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns.

- Dr. Andrew Bonthius, F.A.C.P., Pasadena, Calif., February 24, 1957
- Dr. Richard Newnham DeNiord, F.A.C.P., Buffalo, N. Y., March 22, 1957
- Dr. Earl Edwin Farnsworth, F.A.C.P., Santa Barbara, Calif., December 31, 1956
- Dr. Byrl Raymond Kirklin, F.A.C.P., Rochester, Minn., March 2, 1957
- Dr. James Farrar Lewis, F.A.C.P., Columbus, Miss., February 15, 1957
- Dr. Homer Clayton Marshall, Associate, Springfield, Mo., February 23, 1957
- Dr. Leon Arthur Salmon, F.A.C.P., New York, N. Y., January 12, 1957
- Dr. Isadore Simon Trostler, F.A.C.P., Chicago, Ill., Date not known at College Office
- Capt. Walter Alfred Vogelsang, F.A.C.P. (MC, USA, Ret.), San Diego, Calif., February 27, 1957
- Dr. J. Russell Verbrycke, Jr., F.A.C.P., Washington, D. C., February 5, 1957

The College headquarters at 4200 Pine Street, Philadelphia 4, Pa., would appreciate it if members and readers would send in notices of the deaths of members promptly, so that suitable obituaries may be prepared and published. Frequently, deaths of members are not reported for several weeks or even months after a member is deceased.

DR. GEORGE FREDERICK STRONG

The sudden tragic death of Dr. George F. Strong, in Montreal on February 26, 1957, was a great loss to The American College of Physicians, to medicine in general, and to his legion of friends. The cause of death was coronary artery disease.

It is impossible here to do justice to all his accomplishments and good works. The many honors conferred on him acknowledged only a few of his labors. Life for him was a never ending series of obligations and duties, which he gladly undertook.

Dr. Strong was born in St. Paul, Minnesota, on February 22, 1897. He attended The University of Minnesota, obtaining his B.Sc. in 1918, and M.D. in 1921. He served internships at the University Hospital, Minneapolis, and the Vancouver General Hospital. In the Peter Bent Brigham Hospital, he was a Graduate Assistant, 1922 to 1923. He held a Fellowship of The National Research Council at Harvard Medical School in 1923.

Returning to Vancouver, B.C., in 1924 he entered practice in internal medicine and cardiology. He was on the Attending Staff of the Vancouver General Hospital, and was a driving force in its development, for over 30 years. He became Senior Physician and Director of the Out-patient Department. He was a member of the Medical Board from 1936 to 1946. From 1946 to 1951 he was Chief of Medicine, from 1954 to 1956 Chairman of the Medical Board, and from 1930 to 1954 Director of the Heart Station.

Dr. Strong was one of the most active spirits in the formation of the new Medical School at the University of British Columbia. He became the first Clinical Professor of Medicine in 1951, which post he held until his death.

In close coöperation with the Vancouver General Hospital, he was one of the founders of The British Columbia Cancer Institute; and a Founder and Chairman of the Medical Board of the British Columbia Medical Research Institute.

He was elected to many posts of honor. He was a Past President of The Vancouver Medical Association, The British Columbia Medical Association, The Canadian Medical Association, The North Pacific Society of Internal Medicine (a Founder), and The Canadian Heart Association. He was also a member of The Pacific Interurban Clinical Club, The American Heart Association, The International Heart Association, The British Cardiac Society and The British Columbia Society of Internal Medicine. In 1938 he became a Diplomate of The American Board of Internal Medicine.

In help to community affairs he gave much of himself. He was a former Director and a Past President of the Community Chest of Vancouver and a Founder and Vice President of The Western Society for Rehabilitation. Almost single handed he fostered and launched the latter institution. In addition, he had been a member of the Founding Committee and First President of The Quilchena Golf Club; a member of The Founding Committee and First President, later Honorary President, Family Service Agency of Greater Vancouver; Past President Greater Vancouver Health League; Former Director and Past President, Council of Social Agencies; and Director of the British Columbia Division, Canadian Cancer Society.

Nationally and internationally known and respected, he held Fellowships in The Royal College of Physicians (Canada), The Royal College of Physicians (London) and The Royal Australasian College of Physicians. Honorary degrees were bestowed upon him by three Canadian Universities: The University of British Columbia (D.Sc.), Laval University (D.Sc.) and The University of Toronto (LL.D). He was honored by the Vancouver Medical Association with the "Degree of Prince of Good Fellows."

The American College of Physicians was always dear to his heart. He became a Fellow in 1937, was Governor for Western Canada (1939 to 1941), Regent (1941 to 1950), Vice President (1944 to 1950), President (1955 to 1956), and Regent at the time he died.

His contributions to medical literature were numerous. His chief interest lay in Cardiology, as reflected in his writings.

It would seem that with his tremendous capacity for work, he believed, for himself (to quote from one of his published papers), that "There is little evidence of effort and strain as a precipitating factor in coronary artery occlusion."

Many of his colleagues will have happy memories of good companionship, travel, banter, and discussions; occasionally spirited and even bitter debate; for he always stood up for his principles. Many a one who depended on him will realize with a pang that his advice and wise council are no longer available. A skillful clinician, consultant and teacher, with a kind heart and a clear courageous mind, he gave his considered opinion without fear or favor.

He was not spared sorrow and tragedy, but his undaunted spirit met them unflinchingly and with harder tasks for himself, in the service of others. His only son was killed in action in 1942. He himself, as he wished, died in action, for he was on his way to attend a meeting as First President of The National Heart Foundation of Canada.

His wife and daughter who survive him can take some comfort in the great heritage of service and devotion to duty that he leaves behind him. The following lines from Tennyson seem appropriate.

"Self reverence, self knowledge, self control,
These three alone lead life to sovereign power
Yet not for power,
Power of herself, would come uncalled for,
But to live by law,
Acting the law we live by, without fear,
And because right is right, to follow right,
Were wisdom, in the scorn of consequence."

H. A. DESBRISAY, M.D., F.A.C.P., Governor for British Columbia

DR. ROBERT WARREN BLUMENTHAL

Dr. Robert Warren Blumenthal, F.A.C.P., died on July 1, 1956, after a prolonged terminal illness due to diabetes mellitus and arteriosclerosis. He was born in Columbus, Wisconsin, in 1881 and received his M.D. degree from the University of Illinois College of Medicine in 1904. His hospital training was done in Philadelphia and Boston, after which he entered the clinical practice of internal medicine in Milwaukee in 1906. Except for periods of military service in both World Wars, he continued in clinical practice until his retirement in 1950.

He served on the faculty of Marquette University School of Medicine and on the medical staffs of Milwaukee, St. Luke's, Evangelical Deaconess, and Milwaukee County Hospitals. For many years he was chief of the Department of Internal Medicine of Milwaukee Hospital. He served as President of the Medical Society of Milwaukee County and of the Milwaukee Academy of Medicine. He was a member of both of those organizations, of the State Medical Society of which he was a member of the Council for several years, American Medical Association, and a Fellow of The American College of Physicians. He was Editor of The Milwaukee Medical Times for more than ten years and participated in the compilation of the contributions of Wisconsin physicians in the military services, which was published under the title "War without Guns."

For many years Dr. Blumenthal occupied a position of prominence in the medical profession as well as the entire community. He made a number of important contributions to medical practice, for which he will long be remembered. He is survived by his wife, daughter, and four grandchildren.

Frederick W. Madison, M.D., F.A.C.P., Governor for Wisconsin

DR. DOUGLAS BOYD

Dr. Douglas Boyd, F.A.C.P., died suddenly on December 21, 1956, while making rounds in the Highland Park Hospital, Highland Park, Ill. He was Chairman of the Department of Internal Medicine at the Highland Park Hospital.

Dr. Boyd was born at Griffin, Ga., and attended the University of Georgia. He received his M.D. degree from Harvard Medical School in 1922. He served his internship at the Peter Bent Brigham Hospital in Boston, 1923–24. From 1924–25 he served as an associate and assistant resident at the Hospital of the Rockefeller Institute in New York City. During 1925, Dr. Boyd served as an assistant resident at the Lakeside Hospital, Cleveland, Ohio.

He was a Diplomate of the National Board of Medical Examiners and of the American Board of Internal Medicine. At one time he was on the faculty of Northwestern University Medical School. Besides his service at the Highland Park Hospital he also served on the attending staff of the Lake Forest Hospital, Lake Forest, Ill. At one time he was President of the Highland Park Board of Health.

Dr. Boyd was a member of the Lake County Medical Society, Illinois State Medical Society, American Medical Association, and the American Rheumatism Association. He became a Fellow of the American College of Physicians in 1941.

Dr. Boyd was deeply interested in general internal medicine, but his special interest was rheumatic diseases. He was a hard worker and devoted to his patients. His sudden death was not only a great shock to his devoted family, but to the whole community in which he was a leader. His family, patients, and colleagues will miss him.

Survivors include his widow, Marion, a daughter, Ann, and a son, David. His widow, Mrs. Marion Taylor Boyd, lives in the family home at 999 Wade St., Highland Park, Ill.

HOWARD WAKEFIELD, M.D., F.A.C.P., Governor for Northern Illinois

DR. CHARLES E. BOYNTON

On November 22, 1956, Dr. Charles Edward Boynton answered his last call. He passed away at the home of his daughter, Dr. Estelle Boynton on Avery Drive in Atlanta, Ga. Dr. Boynton had enjoyed a long and interesting career in the practice of pediatrics in Atlanta. He was 84 years old at the time of his death.

Charles Edward Boynton was born in Atlanta, April 21, 1872. In September of 1889 he enrolled in Princeton University, graduating from that institution with a degree of Bachelor of Arts in June, 1893. He entered the College of Physicians and Surgeons of Columbia University in 1893 and was graduated with a degree of Doctor of Medicine in 1896. After graduating from medical school he served an internship at Bellevue Hospital in New York City, finishing in 1898. After his internship he joined the services of his country as Assisting Surgeon, stationed on the hospital ship Missouri during the Spanish-American War. Upon his return from the war, he married Miss Estelle Pattillo of Decatur in 1899. This union was blessed with three children: Charles Edward Boynton, Estelle Pattillo Boynton, and Myra Louise Boynton (Mrs. James Randolph Brown).

Dr. Boynton began his practice in 1900. His activities included Visiting Physician at McVickers Hospital, Spelman University, Wesley Memorial Hospital, and Grady Hospital. He was also Visiting Physician at Piedmont Hospital and St. Joseph's Hospital, and Vice President of the Medical Staff of Good Samaritan Clinic. His teaching career included Chairmanship of the Department of Pediatrics (1904–1919) at what is now Emory University, as well as lecturer and Associate Professor of Medicine. He was a member of many medical societies and specialty groups, including the American Board of Pediatrics and the American College of Physicians. His medical fraternity was Phi Chi. His published articles were found often in the various medical journals.

He was a member of the Trinity Methodist Church and served as Chairman of the Board of Stewards in this church.

CARTER SMITH, M.D., F.A.C.P., Governor for Georgia

DR. ROBERT EMMET BRITT

Dr. Robert Emmet Britt, F.A.C.P., died suddenly of myocardial infarction at his home in St. Louis, Missouri on October 28, 1956. He was born in Omaha, Nebraska on March 9, 1904. He received his M.D. degree from Creighton University in 1929.

After a year of internship at the Highland Hospital in Oakland, California, Dr. Britt served two years as resident in Psychiatry at the Boston Psychopathic Hospital. This was followed by an additional two years of postgraduate study in Psychiatry at Montefiore Hospital and Vanderbilt Clinic in New York City. He was a diplomate of the American Board of Psychiatry and Neurology.

In 1935, Dr. Britt was appointed Instructor in Neuropsychiatry at St. Louis University School of Medicine and was advanced to Assistant Professor of Clinical Neuropsychiatry in 1945 and to Associate Professor of Clinical Psychiatry in 1952. For more than ten years before his death, Dr. Britt had been a member of the Administrative Committee of the Department of Neuropsychiatry.

Dr. Britt was a member of the staffs of the St. Mary's Group of Hospitals, the St. Louis City Hospital, St. John's Hospital, Deaconess Hospital, St. Vincent's Sanatorium and Alexian Brothers Hospital. He was a member of the American Medical Association, American Psychiatric Association and Central Psychiatric Association. He was a past president of the Missouri Society for Neurology and Psychiatry. He was appointed a Fellow of the American College of Physicians in 1940.

After coming to St. Louis, Dr. Britt married Dorothy Dierker and in the years that followed, six children came to their home. The last several hours of his life were spent with two of his children attending one of their school activities.

Dr. Britt's professional career was characterized by a deep sense of responsibility for his patients and he spared neither time nor effort in attempting solution of the difficult problems typically found in his clinical field. He will long be gratefully remembered by the many patients to whom he was able to bring confort in their time of distress as well as by the large numbers of students who benefited from his instructional activities.

G. O. BROUN, M.D., F.A.C.P.

DR. RICHARD DEXTER

Dr. Richard Dexter, A.B., M.D., F.A.C.P., a member of the Cleveland Academy of Medicine since 1910, passed away after a prolonged illness on January 19, 1957. He was born in Massachusetts, September 19, 1878.

He was graduated from Harvard College in 1901, and from the Harvard Medical School in 1905. He interned at the Massachusetts General Hospital, and then did postgraduate study in Europe at the Allgemeines Krankenhaus and the Adolph Schmidts Klinic. Upon the completion of his postgraduate studies, he assumed the position of instructor in Physical Diagnosis at the Cleveland City Hospital, and joined the faculty of Western Reserve University School of Medicine in 1910. He served consecutively as demonstrator in Medicine, instructor in Medicine, and associate in Medicine during the ensuing decade. He entered service during World War I, with the Lakeside Unit. He was later transferred to the Chemical Warfare Service as Medical Consultant, and was discharged in 1919 with the rank of Brigadier General. Returning to Cleveland, he resumed his teaching, until invited to join the staff of St. Alexis Hospital, in which capacity he remained active until illness forced him to retire. As Director of Medicine and later as Chief of Staff, he was instrumental in its reorganization. In addition to his professional work, he was very active in Academy affairs, having served on many important committees and the Board of Directors. In

1929, he was elected President of the Cleveland Academy of Medicine. He became Medical Director of the East Ohio Gas Company. He was a diplomate of the American Board of Internal Medicine, and a Fellow of the American College of Physicians since 1930. He was a member of the Society for the Advancement of Clinical Investigation, as well as of national, state and local societies, and was the author of a number of published papers.

He is survived by a son, daughter, and two grandchildren.

His scholarship, teaching ability, and intense interest in promoting the high standards of his profession, will stand as a tribute always to his memory.

CHARLES A. DOAN, M.D., F.A.C.P., Governor for Ohio, A.C.P.

DR. DANIEL P. FOSTER

Dr. Daniel P. Foster, F.A.C.P., of Detroit, Michigan, died August 21, 1956, at the age of 64 years. He had been in chronic ill health and semi-retirement for several years because of Parkinson's disease, which was the cause of his demise.

Dr. Foster was born in Progress, Oregon. He obtained his academic education at the University of California, receiving a B.A. degree in 1917 and an M.A. degree in 1918. During the latter year he became a member of the resident staff of the George Williams Hooper Foundation for Medical Research. His work in this position was under the guidance of Dr. G. H. Whipple. The two collaborated in the publication of several papers concerning blood fibrin.

After obtaining his medical degree from Harvard Medical School in 1922, Dr. Foster served his internship at the Massachusetts General Hospital, Boston. In 1923 he joined the medical staff of the Henry Ford Hospital, Detroit. Subsequently he became Physician-in-Charge, Division of Metabolism in this institution with a major interest in the study and treatment of diabetes mellitus. He participated in the publication of numerous papers on various aspects of this subject. In 1934–35 he served as extramural lecturer in this field at the University of Michigan.

Dr. Foster was a member of a number of professional organizations, including the Wayne County Medical Society, the Michigan State Medical Society, the American Medical Association, the American Diabetes Association, and the Association for the Study of Internal Secretions. He became a Diplomate of the American Board of Internal Medicine in 1939, and a Fellow of the American College of Physicians the same year.

Aside from his achievements in physiology and medicine, Dr. Foster had many other fields of interest, including athletics, civic, and cultural activities. During his undergraduate days at the University of California he was captain of the varsity football team and an all-coast guard in basketball. In 1937–38 he served as physician for the Detroit Lions football team. Dr. Foster was greatly interested in music, was an accomplished pianist and accumulated a large library of symphonic and operatic records. He had served as a member of the Board of Directors of the Detroit Civic Opera, as a member of the Board of Directors of Pro Musica, and was a member of a local dramatic organization, the Players. He also served as a member of the Medical Advisory Board No. 3 for selective service during World War II.

As one interested in research, a contributor to medical literature, and a capable and beloved physician, Dr. Foster was held in the highest esteem by his confreres, friends and patients. It seems particularly tragic that his productive and promising career should have been interrupted by an incapacitating type of chronic illness.

ROBERT H. DURHAM, M.D., F.A.C.P., Detroit, Michigan

DR. SAMUEL A. MUNFORD

Samuel Archer Munford, A.B., M.D., Clifton Springs, N. Y. Born, Princeton, Ind., December 14, 1876; A.B., 1900, Monmouth College (Monmouth, Ill.); M.D., 1905, Jefferson Medical College, Philadelphia; Intern, 1905–06, Jefferson Medical College Hospital; Assistant Demonstrator, Jefferson Medical College, 1906–09; joined the Staff of the Clifton Springs Sanitarium and Clinic, May 1919, and served successively as Director of the Clinic, Associate Superintendent, and Superintendent until 1950; he continued, however, as an active member of the Staff until his retirement in 1954; entered the College first as an Associate through the American Congress on Internal Medicine in 1923, and became a Fellow in 1946; past President of the Ontario County Medical Society; past President, 7th District of the Medical Society of the State of New York; Medical Advisor at Cornell University in Ithaca from 1910 to 1917; Veteran of World War I; died October 29, 1956, aged 79, of hypertensive cardiovascular disease. He is survived by his widow, Mrs. Carolyn Andreas Munford, 2 Highland Place, Clifton Springs, New York.

The death of Dr. Munford ended a long professional career. During his last illness and up to the time of his death he was intensely interested in all of the newer developments in medicine. Those of us who had the opportunity of working closely with him were always impressed with his scholarly and practical approach to the problems of internal medicine. Kindness and understanding toward his colleagues, as well as his patients, made him widely loved and respected by those who knew him. Upstate New York has lost one of the pioneers in the field of Internal Medicine.

BERNARD A. WATSON, M.D., F.A.C.P.

DR. LOUIS HARRY NEWBURGH

Dr. Louis Harry Newburgh, F.A.C.P., died at Valley Center, California, on July 17, 1956, of acute myocardial infarction. Dr. and Mrs. Newburgh had been living in the hills near Valley Center following his retirement as Professor of Clinical Investigation at the University of Michigan Medical School in 1952.

Dr. Newburgh was born on June 17, 1883, in Cincinnati, Ohio. He received the A.B. degree from Harvard College in 1905 and the M.D. degree from Harvard Medical School in 1908. After an internship at the Massachusetts General Hospital, Dr. Newburgh spent a year in Vienna and then returned to Boston, where he served as an Assistant in Internal Medicine at the Harvard Medical School until 1916. At this time he came to Ann Arbor as Assistant Professor of Internal Medicine in the University of Michigan Medical School, and he remained at Michigan until his retirement in 1952. He was advanced to an Associate Professorship in 1919 and to the Professorship of Clinical Investigation in 1922. During the second World War Dr. Newburgh carried out special work for the U. S. Government and was away from Ann Arbor on leave of absence during several of these years. Much of the work he did during this period was confidential, but his knowledge of heat production and regulation in the human body made it possible for him to contribute much in the design and construction of suitable clothing for troops exposed to heat or cold.

Dr. Newburgh was interested primarily in metabolic and kidney diseases, and his most important early work was the development, with Dr. Phil Marsh, of low carbohydrate, high fat diets for the treatment of diabetes mellitus. After the discovery of insulin these diets were no longer necessary, and Dr. Newburgh thereafter devoted most of his time to experimental and clinical studies on nephritis, water and electrolyte balance, obesity and heat production. He was the author of many papers and several books on these subjects.

Although his research activities were important, Dr. Newburgh's greatest contributions were probably as a teacher and as an inspiration to young physicians to do research work. His lectures were beautiful in their logic and clarity, but he

was most at home in the laboratory. Many of his former students will remember how he led them from the ward to the nearest laboratory where he took great delight showing them how to examine a urine specimen or to do some other test properly. He was intolerant of careless work or sloppy thinking and was likely to be pretty rough with students when he detected these faults. On the other hand, when a student or young physician showed a sincere interest in a research problem, Dr. Newburgh would do everything possible to encourage and support him. The late Dr. Ferdinand Schemm was one of many young physicians who were inspired to do research work by Dr. Newburgh.

He was a member of many important societies and organizations, including the following: American Society for Clinical Investigation, Association of American Physicians, American Medical Association, Society for Experimental Biology and Medicine, American Diabetes Association and he was a Fellow of the American College of Physicians since 1930. He was also a Diplomate of the American Board of Internal Medicine, and for several years was Associate Editor of the Journal of Nutrition.

Dr. Newburgh was a complicated person with a brilliant mind, great devotion to his work and complete loyalty to his friends. He found pleasure and relaxation working out-of-doors, usually with Mrs. Newburgh at his side. The beautiful garden flanked by stone walks and walls, all created by the Newburghs, will be remembered by many friends who visited their home on Geddes Avenue east of Ann Arbor. After his retirement Dr. Newburgh largely gave up his medical work, but he continued to work tirelessly in the garden of the new home in the hills near Mt. Palomar. His last few years were greatly saddened by the death of his youngest son, David. Dr. Newburgh is survived by his wife, Irene, and his other son, Henry. Their address in 809 N. Sanders Avenue, Ridgecrest, California.

Franklin D. Johnston, M.D., F.A.C.P., Ann Arbor, Michigan

DR. HARRY EVANS PATRICK

Dr. Harry Evans Patrick was born in Jackson Center, Michigan on March 10, 1884, and graduated from the University of Michigan Medical School in 1909. He was affiliated with the Youngstown Hospital Association during his entire medical career. He served as an intern from 1909 to 1910, was a member of the adjunct staff from 1910 to 1916, and became a member of the active staff in October, 1916. He served the hospital in many capacities; he was a member of the committee that wrote the first constitution for the Medical Staff on November 21, 1916, was Chief of Obstetrics from 1921 to February 1950, and also served on the executive committee from January 17, 1930 to February 1950, then becoming a member of the emeritus staff. He was a trustee of the Associated Hospital Service from 1938 to 1956, and was its President since March 1, 1950.

In addition to his medical activities, he served on the Youngstown Board of Education from 1933 to 1949, and was President from 1942 to 1949.

He became a Fellow of the American College of Physicians in 1920. He was very much interested in obtaining the latest medical literature and books for the staff. He was the founder and organizer of the library of the Youngstown Hospital Association, and spent many hours in compiling and systematizing the journals and books in our Medical Library.

He died at the Youngstown Hospital, September 28, 1956, following an abdominal operation.

He was a beloved and devoted father and spent considerable time in raising a large family. He is survived by his wife, two daughters, and four sons, two of whom. Dr. James Patrick and Dr. Gilbert Patrick, are practicing physicians.

CHARLES A. DOAN, M.D., F.A.C.P., Governor for Ohio 27 rteriosclerosis of the central nervous system is the commonest cause of vertigo that we see. . . . It is usually mild, is often positional and responds poorly to treatment. Dramamine and sedation are often beneficial...."

Lewis, M. L., Jr.: The Problem of the Dizzy Patient, New Orleans M. & S. J. 104:161 (Oct.) 1951.



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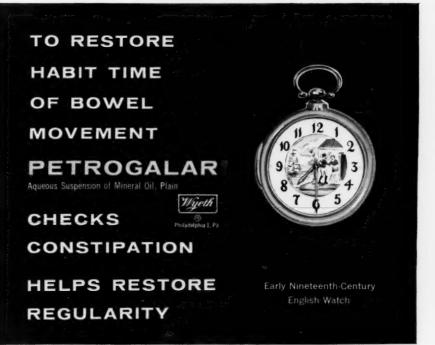
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Marquis, D. G., Kelly, E. L., Miller, J. G., Gerard, R. W. and Rapoport, A.: Ann. New York Acad. Sc. 67:701, May 6, 1957.

"Since it [meprobamate-'Miltown'] does not cloud consciousness or lessen intellectual capacity, it can be used ... even by those busily occupied in intellectual work."

Keyes, B. L.: Pennsylvania M. J. 60:177, Feb. 1957.

"...the patient never describes himself as feeling detached or 'insulated' by the drug ['Miltown']. He remains completely in control of his faculties, both mental and physical ..."

Sokoloff, O. J.: A.M.A. Arch. Dermat. & Syph. 74:393, Oct. 1956.

"It ['Miltown'] ... does not cloud the sensorium, and has a helpful somnifacient effect devoid of 'hangover'."

Kensler, L. N. and Barnard, R. D.: M. Times 84:431, April 1956.

"In anxiety and tension states, meprobamate relaxes without dulling cortical function to the same extent as the commonly-used barbiturates."

Rindskopf, W., Ravreby, M., Gutenkauf, C. and Sands, S. L.: J. Iowa M. Soc. 47:57, Feb. 1957.

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*Dodd, M.C., and Stillman, W.B.: The in vitro bacterlostatic action of some simple furan derivatives, J. Pharm., Exp. Ther. 82: 11, 1944.

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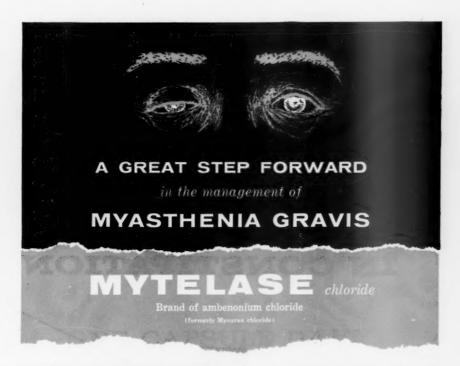
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 Schwab, R.S.; Marshall, Clare K.; and Timberlake, William: J.A.M.A., 158:625, June 25, 1955.

2. Schwab, R.S.: Am. Jour. Med., 19:734, Nov., 1955.

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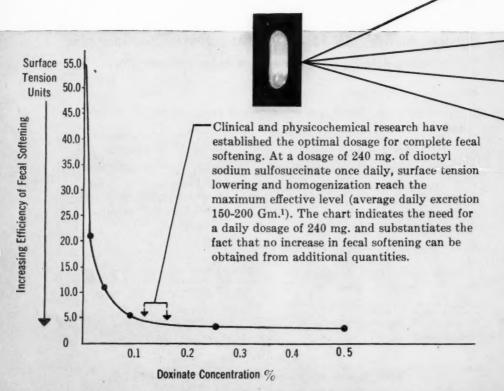
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1. Best & Taylor, The Physiological Basis of Medical Practice, 6th Ed.

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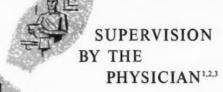
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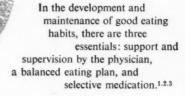
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- 1. Eisfelder, H.W.: Am. Pract. & Dig. Treat. 5:778 (Oct. 1954).
- 2. Freed, S.C.: G.P. 7:63 (1953).
- 3. Sherman, R.J.: Medical Times, 82:107 (Feb. 1954).

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(1) King, J. W., and Hainline, A., Jr.: Commercial Glucose Oxidase Preparations for the Detection of Glucose in Urine, Cleveland Clin. Quart. 23:212, 1956. (2) Leonards, J. R.: Evaluation of Enzyme Tests for Urinary Glucose, J.A.M.A. 163:260 (Jan. 26) 1957.

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References: 1. Borrus, J. C.: M. Clin. North America, In press, 1957. 2. Gillette, H. E.: Internat. Rec. Med. & G. P. Clin. 169:453, 1956. 3. Pennington, V. M.: J.A.M.A., In press, 1957. 4. Cayer, D.: Prolonged Anticholinergic Therapy of Duodenal Ulcer. Am. J. Dig. Dis. 1:301-309 (July) 1956. 5. McGlone, F. B.: Personal Communication to Lederle Laboratories. 6. Texter, E. C., Jr.: Personal Communication to Lederle Laboratories. 7. Bauer, H. G. and McGavack, T. H.: Personal Communication to Lederle Laboratories.

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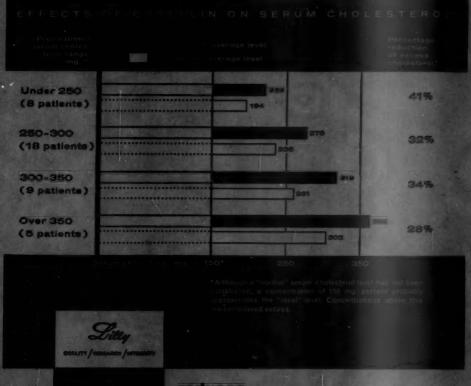
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